

Scandinavian journal of clinical &
laboratory investigation : Suppl.

[no. 19]

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THE INFLUENCE OF
HEAVY HYDRATION ON THE
RENAL FUNCTION IN NORMAL
AND HYPERTENSIVE MAN

BY

JAN EK

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STOCKHOLM 1955

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AKADEMISK AVHANDLING

som med tillstånd av Kungl. Karolinska Institutets lärar-
kollegium för ernående av medicine doktorsgraden
offentligen försvaras i Fysiologiska institutionens
föreläsningssal onsdagen den 4 maj 1955 kl. 9 f. m.

AV

JAN EK
MED. LIC.

FROM THE CENTRAL LABORATORY, ST. ERIKS HOSPITAL, STOCKHOLM, SWEDEN

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ALSO PUBLISHED AS A SUPPLEMENT TO VOL. 7 OF
THE SCANDINAVIAN JOURNAL OF CLINICAL AND
LABORATORY INVESTIGATION 1955

ESSELTE AKTIEBOLAG

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AND HYPERTENSIVE MAN*

BY

JAN EK

* All my patients with arterial hypertension have come from the IVth Medical Service, S:t Eriks hospital. For this, and for valuable assistance in other ways I am deeply indebted to the head of that Service, Docent Ebbe Nyman.

I extend my thanks for helpful co-operation and advice to Docent Härje Bucht and Docent Lars Werkö of the same Medical Service. The latter has carried out or directed the catheterizations of the renal vein which are included in the present investigation.

Technical assistance has been given by Mrs Anna-Brita Olsson, Miss Ester Strandberg, Miss Inga Landbrink and Mr George Engström.

The English translation is the work of Mrs Elspeth Harley Schubert.

The typing of the manuscript has been carried out by Mrs Eva v. Bonsdorff, whose help in many other ways has also been invaluable.

The investigation has been undertaken with the financial aid of *Institutet för Malt-drycksforskning* and *Statens Medicinska Forskningsråd* to both of which institutions I wish to offer my sincere thanks.

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INTRODUCTION

For several years the excretion mechanism and hemodynamic of the kidneys have been studied at the Central Laboratory, St Erik's Hospital, Stockholm, in co-operation with the IV:th Medical Service of the said hospital; the excretion of water and strong electrolytes has thus, inter alia, been studied in healthy man and in patients with disturbances of the renal function and the general blood circulation. In patients with mitral stenosis and arterial hypertension it was therewith observed that both the clearance values (p-aminohippuric acid, inulin, creatinine) and sodium and chloride excretion seemed to be characteristically influenced by the size of the diuresis (or the hydration). This became especially clear when we attempted to apply to a clinical material our own earlier findings with regard to the effect of peroral loading with beer on the renal sodium excretion (Ek, Josephson 1953 a). We had found earlier that beer in normal persons has a specific natriuretic effect. This had later been adapted clinically to cases of circulation insufficiency (Wallgren 1954, Olmstead, Cassidy and Murphy 1954).

The conditions precedent for these experiments were not, however, intended for or suited to a study of the effect of acute hydration on the kidney function. The investigations reported in this paper are intended to illustrate directly the effect of strong, acute hydration both on normal persons and on patients suffering from arterial hypertension. Analogous studies on patients with mitral stenosis have also been undertaken; these have been preliminarily reported. (Werkö, Ek, Bucht and Varnauskas 1954). These latter results will only be considered in the final discussion in this paper.

Acute fluid loading has been used throughout; a certain, comparatively large and carefully controlled fluid volume was given intravenously or perorally during a period of about two hours. Both fluid supply and urine production are therewith easier to check than during lengthy experiments. (This does

not, of course, eliminate the value of lengthy loading experiments — it is possible that these latter constitute an entirely different problem.)

Cases of uncompensated hypertension have been excluded, for the reason that their “initial” hydration conditions are more uncertain, and because uncompensation itself may constitute a basically new factor in the salt and water metabolism.

The attempts to study how far acute hydration resp. acute changes of the diuresis affect the kidney function in healthy man and in patients with arterial hypertension, which will be accounted for here, can be divided into three main groups:

1. Considerable quantities of diluted glucose solution were given intravenously at an even speed.
2. Beer resp. water was given by mouth in a large and standardized quantity within two hours.
3. During the course of strong hydration (as under 1) a theophylline diuretic was given. Our previous experience has shown (Ek and Josephson 1953 b) that theophylline gives an extremely rapid and effective, although often relatively short, increase of diuresis. The diuretic effect of theophylline seems to develop more rapidly than with any other known diuretic.

EARLIER STUDIES

I. Clearances, diuresis and electrolyte excretion in normal man

All the important literature on these subjects can be found in the monographs of Smith (1951) and Wolf (1950) and others, and no attempt to sum it up will be undertaken. Despite this, however, some of the work which has been published from the Central Laboratory of St Erik's Hospital will be given special mention—not because it is of more interest than other research in this field, but because as regards technical methods, the choice and control of normal subjects and the routine system of diagnosis is in all essentials comparable with the present paper.

Concerning the "basal" clearance values in normals, see Bucht (1951).

Concerning the renal extraction of para-amino-hippuric acid (= PAH) see Josephson, Ek, Bucht, Werkö, Kallas and Grieg (1953).

Concerning the clearance, diuresis and electrolyte excretion of normals during peroral loading with water resp. beer, see Ek and Josephson (1953 a and b).

II. The kidney function in patients with arterial hypertension

A. Clearance values

As it has long been known that there is a connection between kidney disease and arterial hypertension, it is not surprising that a considerable number of different clearance studies have been made on such patients. Before some of these results are briefly reported, two basic remarks should be made: It is highly debatable as to whether any sort of mean value for clearance results should be given in a material of arterial hypertension—even if the standard deviation is presented. This may be considered a superfluous statement; nevertheless this error occurs in a number of papers, despite the fact

that hypertension is a progressive illness, and also that the relation between severe and benign cases must necessarily vary from one investigation to another.

A basic question of greater importance is, however, the following: have the clearance values in a patient with hypertension the same significance as in a normal? Concerning the PAH (or diodrast) clearance as a measure of the renal plasma flow (RPF) the answer is relatively simple. Bradley, Curry and Bradley (1947) and Bradley, Bradley, Tyson, Curry and Blake (1950) found that PAH clearance—as in the case of normals—was about 90 per cent of the plasma flow through the kidneys, determined by means of renal vein catheterization. In “advanced” cases, however, where PAH clearance was less than c. 300 ml/min the renal extraction was lower than normal. Reubi and Schroeder (1949) and Cargill (1949) obtained mainly analogous results. Our own experience (Bucht, Werkö, Ek 1953) and the few experiments presented in this paper confirm this. Summarizing, it may be said that PAH clearance reflects RPF in cases with hypertension as closely as in normals, with one fundamental exception: when PAH clearance falls below c. 300 ml/min a spuriously low RPF will be calculated. There is only one way to determine the latter exactly, i.e. by determining the renal extraction of PAH, an investigation which can scarcely be undertaken as a routine method.

Concerning inulin and creatinine clearance, which have been used to estimate the glomerular filtration, there is even more uncertainty in cases with hypertension than in normals. We know nothing as to whether, or in what degree, inulin resp. creatinine in hypertensives can be transported in or out through the tubular epithelium. However, no proof of such a transport of inulin has been produced, and, in full knowledge of the frailty of the argument, we must temporarily accept inulin clearance as a measure of the glomerular filtration rate.

Following these reservations some clearance determinations in patients with arterial hypertension can be reported: Many subjects classified as arterial hypertension have PAH clearance values within the normal limits. It should be observed that the standard deviation in a normal material corrected to 1.73 m^2 Body Surface Area (= BSA) is considerable, and that patients with hypertension remarkably often have “low normal values”. In many cases, however, particularly in advanced ones, PAH clearance is definitely lower than normal. Hilden (1946, 1948), who classified 60 patients according to Keith, Wagener and Barker (1939) in 4 groups and who determined diodrast clearance in per cent of normal values, has obtained the following mean values: Group I: 78 per cent, group II: 64 per cent, group III: 42 per cent and group IV: 37 per cent. The standard deviations, however, were considerable. Nearly all investigators are in agreement that the renal blood flow is more or less

reduced in cases of arterial hypertension—with the possible exception of the very mildest cases.

It is also unanimously considered that the renal blood flow (examined by PAH or diodrast clearance) sinks earlier during the course of illness, and percentually more than the glomerular filtration rate (examined by inulin, creatinine and urea clearances) so that the filtration fraction increases. In severely damaged kidneys this is not always the case—and, as has already been pointed out, it is doubtful whether in these cases the various clearance values reflect physiological entities such as renal plasma flow and filtration at all. This conception of the clearance values in subjects with hypertension is attributed to the observations of, among others, the following authors: Goldring, Chasis, Ranges and Smith (1941); Reubi and Schroeder (1949), Chasis and Redish (1941); Hogeman (1948). During numerous clinical clearance examinations (unpublished) our results have corresponded to these.

It has long been observed that cases of hypertension show a medial hypertrophy and intimal hyperplasia of the afferent arterioli of the kidney. It might thus be believed that the reduced renal blood flow in arterial hypertension cannot even temporarily be greatly increased. This is, however, entirely erroneous. Various circumstances, procedures, and drugs can increase, and often normalize PAH and inulin clearance in patients with hypertension.

- I. Pregnancy (Bucht, Werkö, personal communication).
- II. Pyrogenes with or without febrile reactions. (Goldring, Chasis, Ranges and Smith 1941).
- III. Spinal anaesthesia (Corcoran, Taylor and Page 1948).
- IV. Apresoline (Reubi 1950).
- V. Lanatoside C (Bucht, Ek, Werkö and Varnauskas, to be published).
- VI. Rapid intravenous infusion (Ek, Bucht and Werkö 1954).

The most striking point about this list is the great diversity of the different agencies. It is probable that by systematic searching the list could be increased still further. We have experience of all the 6 points in the list with the exception of spinal anaesthesia. Apresoline often causes a marked fall in the blood pressure, and the increased renal blood flow is for the most part only registered when the blood pressure is kept up by noradrenaline. Inulin clearance does not then increase. Lanatoside C increases the renal blood flow in hypertensives, to a greater or lesser degree. The increase occurs at most 3 minutes after the injection and lasts for scarcely 10 minutes. The increase of inulin clearance is almost parallel with PAH clearance. Abundant infusion of isotonic glucose solution can sometimes increase the renal blood flow to entirely supernormal values (see Ek, Bucht and Werkö 1954, fig. 4); in the case of a woman with 1.72 m² BSA, PAH clearance rose during two separate short

periods of rapid infusion to 1,664 ml/min and 1,488 ml/min from basal 452 ml/min.

The relation between fluid infusion and the increase of PAH clearance will be discussed in further detail in this paper.

It may even now be pre-supposed, from the various above-named observations, that the kidney vessels in patients with hypertension remain for years under an abnormally high vascular tone, which can be eliminated through a number of seemingly different agents for shorter or longer periods. Inulin clearance then usually increases as much as or more than PAH clearance. This indicates that the clearance changes in arterial hypertension—before the disease has become too far advanced—are functional and not organic, if the word “functional” is taken to mean temporarily reversible. In the later stages of arterial hypertension changes no doubt arise which make it impossible to obtain even a momentary increase to normal values of the renal blood flow or the filtration.

B. Disturbances in salt and water metabolism in patients with arterial hypertension

The blood pressure of chickens which were given salt solution to drink instead of ordinary water rapidly reached pathologically high values in nearly 100 per cent (Lenel, Katz and Rodbard 1948). By giving sodium chloride solution to rats hypertension can also be induced (Sapirstein, Brandt and Drury 1950) but in contrast to chickens only if the salt solution is hypertonic. Dogs and rabbits do not appear to be similarly affected by a salt-containing diet. (Rodbard 1953.)

These data are put forward to illustrate why the salt problem is so actual in the debate on hypertension, but they are also intended to illustrate the striking difference in the reaction of different species to the same substance, or, if one prefers it, the varying etiology of hypertension. For this reason a survey of the ample literature on experimental hypertension in animals must be of limited value for a study of arterial hypertension in man.

Two further reservations must be made; no marked distinction will be drawn between the investigations in which the disturbed salt balance is considered to be a consequence of the process which is the cause of the high blood pressure and those which consider the high blood pressure itself to be a result of the disturbed salt balance. The disturbances in sodium metabolism which are seen in uncompensated cases of hypertension are also ruled out of this discussion.

It is a remarkable fact that “essential” hypertension is a common disease

in "civilized man"—and is rarely to be found among animals and "truly primitive" races (Dahl 1954). The latter author considers that this difference in frequency is to be explained by the high salt consumption of "civilized man" and he has attempted to show, in co-operation with Love (Dahl and Love 1954) that if human beings are divided up into three categories with "low", "average" and "high" salt consumption, the frequency of hypertension is clearly greater for the last group. A number of critical objections can be raised to this assertion. Investigations which try to show that patients with arterial hypertension benefit from a drastic reduction of salt consumption appear to be much more reliable. (Kempner 1949 and many others.)

Thompson, Silva, Kinsey and Smithwick (1954) have drawn attention to the fact that patients with arterial hypertension react to a standardized salt loading in another way than do normal subjects. In normals surgery only slightly changed the salt excretion following the load. Hypertensive patients, on the other hand, excrete a considerably smaller amount of the administered load of extra salt after surgery than before it (the excretion was measured for 3 hours after the salt was given).

Brodsky and Granbarth (1953) found that patients with arterial hypertension excreted very much more sodium during mannitol diuresis than is the case with normals.

Farnsworth (1946) found an apparently good correlation between water diuresis and sodium excretion in hypertensives, but not in normals. Her investigation has been severely criticized (Smith 1951). This will be further discussed later on in this paper.

From these observations and suppositions the conclusion may be drawn that the salt-water metabolism is disturbed in patients with arterial hypertension—whether such disturbance is a part of the etiology of the hypertension itself, or a consequence of the latter.

METHODS

I. Chemical Methods

The methods used in the determination of the different concentrations are presented in Tab. 1. All these methods have long been in use at The Central Laboratory, St Erik's Hospital, where we have gained much practical experience from them.

Table 1. The methods used for determination of relevant substances. About the errors of determination see text!

Substance determined	Method	Error of determination (%) *
Na and K	Flame photometer ("Weichselbaum-Varney")	2.0 (Na) 3.1 (K)
Cl ⁻	Brun (1949)	1.2
Glucose, blood	Folin, micro	—
Glucose, urine	Benedict	—
Creatinine	Jaffé reaction (sat. picric acid)	2.2
Inulin	Corcoran & Page (mod. by Josephson & Godin 1943)	2.6
PAH	Smith, Finkelstein, Aliminosa & Crawford (1945)	1.9
pH	Electrometrically ("Rørpotentiometer")	—
Haemoglobin	Blood 1/200 in 0.1 % solution of Na ₂ CO ₃	—

Column 3, Tab. 1 shows the standard deviations of measurement (in per cent) for the more important methods of determination. In order to prevent subjective influence when checking, the following procedure has been adopted:

a) In the case of samples where duplicate determinations have not ordinarily been used (sodium and potassium) 25 codemarked duplicate samples have

* The "error of determination" is for the sake of consequence estimated for one single determination. When duplicate analyses were made by routine the "error of determination" therefore should be divided $\sqrt{2}$.

gone to analysis without it being possible for the technicians to decipher the code. The standard deviation of measurement for the determinations is then calculated according to current methods.

b) In the case of samples where duplicate analyses were made by routine: (In the present paper duplicate values which diverge more than 10 per cent from each other have been rejected. Among 100 consecutive duplicate values of PAH analysis there appeared 1 pair which diverged more than 10 per cent. The corresponding figure for creatinine analysis was 4, for inulin 3, and for chloride 0) for each method 35 duplicate determinations were carried out and the standard deviation of the determinations was calculated from the first 25 results in which the difference between the duplicates was less than 10 per cent. For colorimetric determinations a "Coleman Jr." or a "Beckman B" spectrophotometer was used.

Creatinine analyses

As is well known, the Jaffé reaction is not specific for creatinine. According to Owen, Iggo, Scandrett and Stewart (1954) 97 per cent of the colour in the Jaffé reaction in the urine is due to creatinine—if the enzymatic method of Miller and Dubos (1937) shows correct values. My results confirm those of Owen et al.

In the present paper "creatinine concentration" in serum has not been reported. Neither has the "endogeneous creatinine clearance" been calculated. In certain experiments, however, the relation between creatinine output in the urine and inulin clearance has been followed. It then becomes of interest to know whether the concentration of the Jaffé-positive substances in serum remained steady.

As the extinction values for the Jaffé colour obtained with the filtrate from the ordinary tungstate precipitation with a tenfold dilution are low and therefore comparatively unreliable, the following procedure has been adopted. In each one of 6 cellophane bags was placed 10 ml plasma from a normal person who had received large fluid infusions. The same experiment was repeated with plasma from a patient with arterial hypertension. The intervals between the start of the infusion and the taking of the samples are registered in Table 2. The plasma was ultra-filtered according to a modification of

Table 2. The constancy of Jaffé-reaction colour in plasma. Determination of Jaffé-reacting substances in plasma from two subjects. Deproteinization by ultrafiltration described in text. Negative and positive time refers to the start of the rapid infusion (starting time = 0).

Normal B 5	Jaffé extinction Time, minutes	0.308 — 21	0.300 — 4	0.314 + 17	0.302 + 37	0.308 + 59	0.310 + 93
Hyp. 22	Jaffé extinction Time, minutes	0.341 — 23	0.350 — 1	0.338 + 21	0.344 + 42	0.340 + 56	0.353 + 88

Rehberg's method proposed by Anders Wassén (unpublished): a 40 ml centrifuge tube was filled with a several centimeter thick layer of carefully-washed and dried glass beads. A filled cellophane bag was laid on top of these beads and the tube was spun in the centrifuge (2,500—3,000 revs/min). The clear, protein-free ultra filtrate was collected from between the beads with a pipette. In Wassén's modification—in contrast to Rehberg's method* in our hands—it seldom if ever happened that a cellophane bag burst: the free creatinine passes the cellophane membrane with the same speed as water, even at a high centrifugal force. This has been established by comparing the concentration in the ultra-filtrate first obtained with that in a later portion.¹

The concentration of creatinine in the ultra filtrate, which is approximately 10 times greater than that in the filtrate from the ordinary Folin precipitation, is so high that it can be accurately determined. The filtrate was diluted with equal parts of water and the extinction of the Jaffé colour was determined. The extinction values are shown in Tab. 2. It will be seen that the extinction of the Jaffé-positive material is not demonstrably affected by the moderate increase of the plasma volume, which is a probable consequence of rapid intravenous infusion. This is scarcely surprising, as creatinine is considered to be evenly distributed throughout the total body water, and is rapidly diffusible.

Table 3. The influence of glucose on creatinine determination. The reading was done exactly 15 min. after addition of reagents.

Quotient $\frac{\text{creatinine conc.}}{\text{glucose conc.}}$...	1:0	1:10	1:50	1:100	1:200	1:750
Creatinine Extinction	0.326	0.323	0.325	0.321	0.347	0.360

The influence of glucose on the creatinine determinations has been registered in Tab. 3. Reading have here, as in the case of all the creatinine determinations in this paper, been carried out exactly 15 minutes after the addition of the Jaffé reagent. It should be observed that the ratios between glucose and creatinine which appear in the table corresponds to what has been found in this connection during the present investigations.

*Brandt Rehberg (1943).

¹⁾ With regard to inulin the case is opposite. If the latter was added to serum and ultrafiltered as above a higher concentration was obtained for every successively collected filtrate portion. This does not mean that the inulin is bound in non-filterable form but only that, at least during relatively rapid ultrafiltration, it passes the membrane more slowly than water.

PAH analyses

As has been pointed out by Baldwin, Schreiner, Breed, Wesson and Maxwell (1950), glucose and PAH may form a combination which cannot be determined by current PAH methods. In Table 4 is registered the speed, with which the PAH extinction decreased when PAH was mixed with glucose in the proportions that were used in the experiments included in the present paper.

Table 4. Effect of glucose on PAH determination. 200 mg of PAH were dissolved in 250 ml 5.5 % glucose solution, and was incubated at 37° C. The extinction coefficient was compared with that of a solution of 200 mg PAH in 250 ml water.

Hours incubation in 37° C	0	½	1	2	5	24
Extinction PAH + Glucose						
Extinction PAH + Water	1.0	0.97	0.91	0.79	0.35	0.33

II. Statistical Methods

Current statistical methods have been used. Regarding the various methods "Introduction to Mathematical Statistics" by Paul G. Hoel (1942) is referred to. Where methods have been used which are not mentioned in this book, the origin and derivation of these are given in the context.

III. Arrangement of the Experiments

A. Technique

1. *Intravenous infusion* was given with a specially-constructed pump aggregate. A rotating eccentric disc working at even speed drives the plunger of a hypodermic syringe backwards and forwards a fixed distance and at a constant frequency. When the plunger goes backwards a certain quantity of fluid is sucked up from a storage bottle via a rubber tube. When the plunger is driven forward a corresponding quantity of fluid goes through the tube to a vein needle indwelling in a cubital vein. The direction of current is regulated by conical ground-in gold valves in glass cavities of corresponding form. Any dimension of hypodermic syringe can be used. The rotation speed of the eccentric disc can also be varied. In this way the quantity of fluid delivered per unit of time can be varied within wide limits. However, the quantity per time unit remains very steadily at the pre-set amount. The syringe was usually set to work at the rate of 40 pulsations per minute. By means of the transferring tube system, the pulsations are evened out so that the stream of fluid delivered through the vein needle becomes more continuous. The ability of the pump aggregate to overcome resistance is relatively great.

Should the hydrostatic pressure against which it works be increased by 150 cm water, the flow is reduced by less than 2 per cent.

During the experiments on man, two such pump aggregates were used, the transfer tubes of which were joined in a T-tube, so that the solutions of both went into the same vein needle. The temperature of the fluid used for rapid infusion was thermostatically regulated at 37° C. In some cases the vein needle was replaced by a catheter indwelling in *vena axillaris* or *vena cava inferior*.

2. *Urine samples* were taken through an indwelling soft rubber catheter in the bladder. After the emptyings the bladder was rinsed with air only. One can admittedly obtain more constant clearance values if the bladder is rinsed with water, but at the same time the values of the urine volume will become less reliable, and their eventual errors more difficult to check. As in this paper the volume figures of the diuresis are of basic importance, and as they have generally been high, it has been considered unsuitable to rinse the bladder with a fluid. The errors in the diuresis figures sometimes obtained in this way are usually clearly reflected in the clearance and excretion figures.

3. *Blood samples* were taken via a cannula indwelling in a brachial artery. In some of the experiments samples of renal vein blood were taken. These were obtained by means of a Cournand catheter indwelling in the right renal vein.

B. Procedure

1. *Experiments regarding the acute effect of intravenous fluid supply*

The patient, or the subject of experiment, arrived about 9 o'clock, was in the post-absorptive state, and had generally had nothing to drink since the previous evening. In a few cases it was necessary to give small doses of a sedative and in connection with this 100—500 ml water had been given 2—4 hours before the commencement of the experiment. The influence of the somewhat varying hydration at the commencement of the experiment will be discussed later. The subjects were in a recumbent position throughout the experiment. After the insertion of the artery cannula, the bladder catheter and the infusion needle a priming dose of PAH and inulin was given. The amounts given corresponded to the amounts subsequently given during 15 minutes of continuous infusion. After this priming dose a slow, continuous infusion of PAH (10—15 mg/min) and inulin (40—60 mg/min) was begun. The subject was in a recumbent position, and psychical irritation was avoided as far as possible. After at least 40 minutes of continuous infusion the bladder was emptied for the first time and the "basal" periods started. After 2 or 3

"basal" periods, covering together between 40 and 80 minutes a rapid infusion (about 25 ml/min) of 3—5 per cent glucose solution was started. As will be observed from the experimental technique this did not involve any new interference with the patient—the rapid infusion went into the previously applied vein needle. During this rapid infusion the clearances and excretions were determined from 6 to 10 consecutive periods, during at least 100 minutes altogether.

During the entire experiment the concentrations in plasma of PAH and inulin were fairly even and was for PAH about 2.0 mg per 100 ml. The highest value registered was 3.95 mg per 100 ml. For inulin the concentration was between 15 and 40 mg per 100 ml.

2. *Experiments regarding the acute effect of a purine derivative on strongly-hydrated subjects*

The first part of the experiments was carried out exactly as in procedure 1. After at least 100 minutes of rapid fluid infusion, or after the subject had had high, almost constant diuresis during 4—5 periods, 0.35 g theophylline-1-amino-propanol-(2) (10 ml "Oxyphyllin" Astra) was given through the infusion tube. The injection time was 1—5 minutes. Clearance and excretion values were thereafter followed—during continuous rapid infusion at unchanged infusion speed—for as long a period as the patient showed no sign of irritation or discomfort. These will be discussed later.

3. *Experiments regarding the acute effect of strong peroral fluid supply on electrolyte excretion*

These experiments were carried out on hypertensive patients only. The subjects had taken neither food nor drink since the evening before the experiment. The experiments were started about 11 o'clock. The patients first gave samples of urine by voiding. After this they were given 2 litres of water or fruit juice and water to drink during 2 hours. The quantity of fluid was evenly distributed over this period, usually $\frac{1}{3}$ of a litre every twenty minutes. The patients were required to empty their bladders as often as they could during the 2 hours. At each voiding, time and volume were noted. Blood samples were first taken after the completion of the experiments, in order to avoid mental irritation or pain during the process of experiment. During these experiments the patients were not confined to bed, but were allowed to sit quietly in a separate room.

The same procedure was repeated on one other occasion with the same subjects, there being one difference: on the second occasion they drank the same amount of Swedish Pilsner (Swedish Pilsner Beer, (class II) has an alcohol content of 2.8 per cent v/v) as they had previously drunk water or fruit juice and water.

EXPERIMENTS CARRIED OUT AND MATERIAL

I. Experiments carried out

A. *Intravenous Fluid Supply*

The acute reaction to rapid supply of 3—5 per cent glucose solution was investigated in 6 normal persons and in 22 cases of arterial hypertension. In 3 cases of hypertension complications developed so that the experiments could not be fully carried through.

B. *Experiments with a purine derivative given during strong hydration*

In 5 experiments the acute effect of Oxyphyllin was examined in normal subjects who had achieved a steady »maximal» water diuresis by means of a rapid infusion as described above. Analogous experiments were made on 5 cases of hypertension.

C. *Peroral Fluid Supply*

On 6 cases of hypertension 12 experiments were undertaken in order to study the effect of an acute peroral hydration. These 6 patients were once each given water or diluted fruit juice as a fluid load, and once each beer.

II. Experimental Material

The experiments were carried out on 10 normal persons and on 24 patients with arterial hypertension. The sex, age and body surface area of the normal subjects is shown in Tab. 5. The 24 cases of arterial hypertension are accounted for in Tab. 6 a and 6 b. Several experiments on a number of individuals have been undertaken. The number of experiments made is therefore greater than the number of persons examined. It will be seen from the tables which of these persons have been subjected to several experiments.

Table 6 a includes patients with hypertension which on clinical grounds has been considered as "essential". Concerning the material in Table 6 b (labelled as "nonessential") in one case (14) the hypertension was complicated by mitral stenosis, in one case (10/18) it was probably due to an amyloid kidney cirrhosis, and in 3 cases it was a result of a chronic pyelonephritis (cases 31 and 34) or a glomerulo-nephritis (case 32). In some of the other cases there was certain—although slight—reason to suspect a kidney disease as being the cause of the hypertension. Cases 7 and 8 had been sympatectomized according to Peet, cases 21, 22 and 18 according to Smithwick.

RESULTS

I. Experiments regarding the acute effect of intravenous fluid supply

In each separate experiment the clearances were determined during 9—13 consecutive periods, and a large number of determinations of the different concentrations in the serum were also carried out. To account in detail for every experiment is, for reasons of space, impossible. The material is therefore presented in the following manner:

1. The complete results from one type example in each group are shown: from the normal group, from the group of hypertensives usually called "essential", and from the group in which the hypertension was supposed to be the result of a primary kidney disease (Tab. 7, 8 and 9).

2. Data concerning clearance determinations, excretion values and plasma concentrations in each experiment are summarized in the following manner: the "basal" clearance and excretion values are balanced and put together to one period which is presented in the tables, together with the mean values from the different plasma concentrations of this period. Further to this, corresponding data are analogously combined, during the first 50 minutes of intravenous fluid supply, to one period, and a third clearance period is similarly calculated for the time between 50 and 100 minutes after commencement of the fluid supply. These mean clearance and excretion values are presented in Tab. 10, 11 a, and 12 a. The administered quantities of water, glucose and insulin are to be found in the Tables 5, 11 b and 12 b resp.

Table 5. Some data about the normal subjects. Column 4: BSA in square meters. Column 5: Fluid injection rate during the rapid infusion in ml/min. Column 6: Glucose injected during the rapid infusion in g/min.

Subj. nr.	Sex	Age, years	BSA	During rapid infusion	
				H ₂ O	Glucose
1	2	3	4	5	6
A 1	M	23	1.72	27.2	1.36
A 4	M	20	1.78	28.0	1.54
A 5	M	22	1.91	35.0	1.93
B 1	F	17	1.52	26.9	0.81
B 2	M	17	2.02	29.9	1.50
B 3	F	28	1.61	30.5	0.92
B 4	M	18	1.92	26.7	1.47
B 5	M	22	2.00	28.7	0.86
B 6	F	21	1.61	26.7	0.93

Table 6 a. Some data concerning the patients with arterial hypertension, clinically judged as "essential".

Column 2: age in years. Column 3: BSA in m². Column 4: heart volume¹

Column 5: eye grounds² N = normal. Column 8: (+) = traces of protein.

Column 9: catechols in µg in the 24 hours urine noradrenaline/adrenaline. The 13 patients above the line are those used in the experiments tabulated in table 11 a. Those below the line are used in experiments with "Oxyphyllin" or drinking.

Case Hyp. nr.	Age	BSA	Heart vol ml/m ²	Eye ground	Art. Blood Pressure	Hypert. known (yr)	Protein-uria	Noradr. adr.
1	2	3	4	5	6	7	8	9
1 (♂)	47	1.79	470	IV	220/160—140/100	4	0	68/41
2 (♀)	47	1.60	340	I	205/110—160/95	2	0	18/10
3 (♂)	50	2.00	480	I	180/100—150/90	2	(+)	—
4 (♀)	50	1.75	275	N	185/120—150/100	10	0	—
5 (♀)	56	2.01	415	II	190/130—160/110	15	(+)	—
6 (♀)	44	1.67	350	III	220/140—180/115	1	(+)	27/4,6
7 (♂)	45	1.87	520	II—III	265/165—220/100	5	(+)	34/4,2
8 (♀)	41	1.67	365	II	190/120—180/70	2.5	(+)	14/1,1
11 (♂)	39	1.73	400	III	230/145—230/125	14	+	20/13
15 (♀)	42	1.61	530	IV	235/170—190/120	2	(+)	—
19 (♂)	44	2.06	420	N	185/115—145/80	1/2	+	—
21 (♀)	46	1.58	350	II	175/110—150/105	12	0	—
22 (♀)	52	1.75	470	III	295/150—245/115	10	(+)	—
17 (♂)	34	1.61	550	IV	240/170—210/155	2	+	18/9,4
41 (♂)	48	2.22	690	IV	220/140—200/120	6	+	—
42 (♀)	41	1.79	405	I	200/120—170/100	2	+	—
43 (♂)	66	2.27	510	I—II	205/120—180/105	4	(+)	—
44 (♂)	33	1.96	420	II	230/145—180/120	1/2	0	—

¹ The heart volumes were determined according to the formula of Liljestrand, Lysholm, Nylin and Zachrisson (1939) by the X-ray Department of S:t Eriks Hospital.

² The eye ground findings were classified according to Keith, Wagener and Barker (1939) by the ophthalmologist at S:t Eriks Hospital, Docent T. G. Kornerup.

Table 6 b. Some data on the patients with "non-essential" hypertension. Column 9: non-protein nitrogen in whole blood in mg per 100 ml. Legend otherwise as in table 6 a.

Case Hyp. nr.	Age (yr)	BSA	Heart vol. ml/m ²	Eye grondud	Art. Blood Pressure	Hypertension known (yr)	Proteinuria	NPN
1	2	3	4	5	6	7	8	9
10/18 (♂)	28	1.72	385	IV	245/150—220/110	8	+	35
14 (♀)	56	1.69	500	II	290/150—165/100	5	(+)	31
31 (♀)	43	1.67	375	I—II	240/140—180/100	1/2	+	37
32 (♂)	58	1.80	500	IV	210/120—195/95	1/2	+	47
34 (♀)	59	1.52	410	N	200/140—170/85	3	+	44—93

Table 7. The course of a typical experiment with rapid infusion on a normal subject. Column 1: time, Column 2: diuresis in ml/min., Column 3 and 4: clearances in ml/min., Column 5 and 6: excretion in mg/min., Column 7, 8, 9: μ Eq./min., Column 10, 11, 12 m Eq/lit. Start of infusion marked by horizontal interspace.

	Diuresis	Clearances		Urinary excretion					Plasma conc.		
		Inulin	PAH	Glucose	Creatinine	Na	K	Cl	Na	K	Cl
1	2	3	4	5	6	7	8	9	10	11	12
10.07—10.27	3.6	143	896	0	1.60	756	137	360	133	3.38	102
10.27—10.43	4.3	132	798	0	1.35	524	125	314	131	3.43	102
10.43—10.52	4.6	127	732	0	1.28	562	132	306	134	3.48	103
10.52—11.14	4.2	155	942	9	1.31	536	104	302	134	3.40	101
11.14—11.31	10.9	172	875	48	1.47	499	79	342	131	3.35	98
11.31—11.49	18.2	166	946	122	1.47	649	74	403	128	3.00	97
11.49—12.08	18.1	138	834	114	1.27	609	79	421	126	2.70	97
12.08—12.25.5	19.5	146	966	123	1.40	573	61	440	124	2.40	97
12.25.5—12.42	21.0	153	1,087	134	1.40	537	53	375	123	2.10	97

Table 8. The course of a typical experiment with rapid infusion on a patient with "essential" hypertension. Legend as in table 7.

	Diuresis	Clearances		Urinary excretion					Plasma conc.		
		Inulin	PAH	Glucose	Creatinine	Na	K	Cl	Na	K	Cl
1	2	3	4	5	6	7	8	9	10	11	12
10.28—10.59.5	1.1	50	474	0	0.83	118	69	75	134	3.85	101
10.59.5—11.23	1.1	52	529	0	0.99	119	84	71	135	3.65	100
11.23—11.49	1.4	57	599	12	0.92	152	69	74	136	3.20	100
11.49—12.06.5	3.5	76	581	96	0.99	202	54	92	131	2.80	102
12.06.5—12.23	9.0	59	607	181	1.01	185	56	93	128	2.75	100
12.23—12.43	19.8	62	715	99	1.18	296	57	188	130	2.75	94
12.43—12.53.5	24.9	63	681	167	1.04	398	44	256	129	2.75	92
12.53.5—13.04	28.1	66	724	160	1.14	534	41	294	123	2.65	95
13.04—13.23	25.2	56	659	174	0.92	466	35	252	121	2.75	100

Table 9. The course of a typical experiment with rapid infusion on a patient with "non-essential" hypertension. Legend as in table 7.

	Diuresis	Clearances		Urinary excretion					Plasma conc.		
		Inulin	PAH	Glucose	Creatinine	Na	K	Cl	Na	K	Cl
1	2	3	4	5	6	7	8	9	10	11	12
10.25—10.46	2.4	56	227	0	0.84	377	52	302	129	3.25	102
10.46—11.02	3.8	55	246	0	0.81	506	68	437	126	3.90	106
11.02—11.22	3.8	81	442	0	0.84	513	68	415	128	3.58	105
11.22—11.37.5	8.9	70	339	28	0.89	1045	90	744	126	3.23	102
11.37.5—11.52	16.6	73	276	70	0.99	1204	111	1035	124	2.95	100
11.52—12.09	23.6	73	268	113	0.93	1592	122	1372	123	2.80	98
12.09—12.24	30.2	77	288	109	1.06	1793	133	1647	123	2.78	94
12.24—12.42	31.2	70	289	122	1.03	1971	126	1859	122	2.78	93
12.42—12.57	29.7	74	282	107	1.06	1617	125	1554	121	2.60	94

Table 10. A condensation of the results from the experiments with rapid infusion on normal subjects. The administered amounts of water and glucose are to be found in table 5. Column 2: B = mean of periods before start of the infusion (basal periods); 0—50 = mean of periods during the first 50 minutes following the start of the infusion; 50—100 = corresponding mean for the subsequent 50 minutes. Calculation of means explained in text. Unities for the other columns are identical with those in table 7.

Subj. Nr.	Period	Diuresis	Clearances		Urinary Excretion					Plasma conc.		
			Inulin	PAH	Glucose	Creatinine	Na	K	Cl	Na	K	Cl
1	2	3	4	5	6	7	8	9	10	11	12	13
B1	B	2.1	91	500	0	0.76	447	120	215	138	3.66	103
	0—50	9.9	118	652	7	0.72	433	113	190	130	2.95	100
	50—100	19.4	101	462	52	0.60	335	64	125	127	2.78	100
B2	B	1.4	154	875	0	1.82	227	64	186	132	3.75	102
	0—50	8.6	181	887	7	1.76	263	59	224	120	4.10	100
	50—100	21.3	179	774	66	1.64	263	31	211	118	3.65	100
B3	B	6.7	141	786	0	1.50	380	75	328	125	4.18	111
	0—50	16.0	194	1,018	48	1.62	545	104	499	116	3.83	107
	50—100	32.3	165	826	133	1.44	440	73	364	118	3.75	102
B4	B	4.0	136	828	0	1.74	635	132	332	133	3.41	102
	0—50	9.6	163	920	46	1.69	548	89	337	133	3.38	99
	50—100	19.0	147	929	121	1.64	595	69	420	126	2.48	97
B5	B	1.2	151	1,041	0	1.37	341	148	—	134	3.70	—
	0—50	2.5	186	1,157	4	1.52	320	161	—	127	3.40	—
	50—100	21.9	209	1,261	44	1.32	352	88	—	128	3.27	—
B6	B	3.7	188	718	0	1.05	516	96	—	130	3.37	—
	0—50	15.7	250	802	28	0.91	502	88	—	124	3.05	—
	50—100	27.5	213	908	83	0.76	565	39	—	125	2.58	—

Table 11 a. A condensation of the results from the experiments with rapid infusion on patients with "essential" arterial hypertension. The administered amounts of water, glucose and insulin are to be found in table 11 b. Legend as in table 10. The figures for PAH-clearance in experiments case 11 do not represent PAH-clearance but renal plasma flow estimated with diodast; the figures given in brackets are $0.9 \times$ the value calculated from renal vein cathetrization.

Case Hyp. nr.	Period	Diuresis	Clearances		Urinary excretion					Plasma conc.		
			Inulin	PAH	Glucose	Creatinine	Na	K	Cl	Na	K	Cl
1	Bas	1.1	68	209	0	0.72	88	33		136	3.17	
	0—50	4.9	101	518	0	1.28	397	96		129	2.90	
	50—100	20.7	122	577	0	1.25	789	69		124	—	
2	Bas	1.8	82	419	0	0.75	78	35		140	3.70	
	0—50	7.0	117	646	46	0.84	233	114		141	3.35	
	50—100	29.2	121	577	471	1.04	984	41		132	3.07	
3	Bas	1.6	122	581	0	1.33	44	133		143	3.60	
	0—50	4.3	151	785	3	1.57	156	126		136	3.00	
	50—100	14.6	153	851	0	1.56	665	115		136	2.40	
4	Bas	1.4	69	413	0	0.76	176	44	115	134	3.85	102
	0—50	1.0	85	527	1	0.84	192	33	104	126	2.85	98
	50—100	3.3	93	533	13	0.90	457	32	293	117	3.25	93
5	Bas	1.9	67	302	0	0.85	266	32		139	3.43	
	0—50	3.4	82	397	0	0.96	298	34		136	3.35	
	50—100	11.1	83	380	55	0.92	363	30		136	3.23	
6	Bas	2.2	50	168	0	0.81	212	86		142	3.46	
	0—50	4.4	59	221	0	0.93	299	100		145	3.20	
	50—100	11.1	66	230	3	0.91	613	100		132	2.98	
7	Bas	2.7	64	234	0	0.91	318	65	253	138	3.54	103
	0—50	8.3	108	463	66	1.33	549	85	417	139	3.10	100
	50—100	21.2	94	392	115	1.12	522	71	337	138	2.70	100
8	Bas	9.0	72	325	0	0.85	275	55	204	151	3.53	106
	0—50	8.0	85	390	0	0.88	334	35	267	145	3.00	102
	50—100	18.3	91	437	0	0.99	477	26	394	143	2.80	100
11	Bas	3.2	31	(332)	0	1.06	377	98		137	3.93	
	0—50	5.1	42	(428)	0	1.12	679	108		135	3.32	
	50—100	13.5	58	(509)	2	1.39	1,100	131		131	3.43	
15	Bas	4.5	—	294	0	0.87	463	80		137	2.58	
	0—50	11.1	—	398	20	0.94	904	82		128	2.42	
	50—100	13.2	—	297	33	0.82	1,333	91		122	2.13	
19	Bas	1.6	150	606	0	1.53	351	117	324	131	3.50	100
	0—50	11.9	162	855	58	1.83	583	125	465	125	2.75	105
	50—100	33.3	164	891	216	1.67	608	84	467	120	2.60	100
21	Bas	1.1	51	498	0	0.90	118	75	73	136	3.76	100
	0—50	4.0	64	595	84	0.97	178	61	85	131	2.80	102
	50—100	22.3	62	696	140	1.11	376	49	223	127	2.70	95
22	Bas	3.8	49	259	0	0.80	522	49	410	129	3.00	102
	0—50	7.1	74	413	11	0.97	723	74	565	129	2.60	82
	50—100	24.1	88	486	50	1.17	1,285	88	1,254	127	2.36	95

Tabell 11 b. Infused amounts in the experiments reported in table 11 a. Water in ml/min., glucose in g/min., insulin I.U./min.

Case Hyp. nr.	Infusion rate			Case Hyp. nr.	Infusion rate		
	Water	Glucose	Insulin		Water	Glucose	Insulin
1	24.4	1.22	0	8	28.5	1.43	0.34
2	28.2	1.41	0	11	27.6	1.38	0
3	31.1	0.84	0.61	15	24.6	0.74	0
4	23.4	0.63	0	19	31.3	1.72	0.56
5	26.2	0.71	0	21	30.2	1.66	0.54
6	23.8	1.19	0	22	24.5	1.35	0.49
7	24.8	1.43	0.34				

Table 12 a. A condensation of the results from the experiments with rapid infusion on patients with "non-essential" arterial hypertension. Legend as in table 11 a.

Case Hyp. nr.	Period	Diuresis	Clearance		Urinary Excretion					Plasma conc.		
			Inulin	PAH	Glucose	Creati- nine	Na	K	Cl	Na	K	Cl
10	B	3.0	56	276	0	1.00	434	59	360	129	3.70	103
	0-50	8.0	75	359	31	1.08	900	88	716	125	3.08	101
	50-100	28.4	73	339	115	1.20	1,789	127	1,633	122	2.78	94
18	B	1.4	42	235	0	0.90	192	77	156	134	4.33	102
	0-50	1.9	53	358	0	0.94	200	84	142	124	3.70	100
	50-100	7.2	53	282	0	0.93	298	53	171	126	3.17	96
14	B	1.3	61	337	0	0.79	64	61	—	142	3.70	105
	0-50	6.5	124	384	19	0.92	119	61	—	136	3.36	101
	50-100	22.6	133	409	94	1.03	353	50	—	129	3.13	102
31	B	3.2	33	156	0	0.69	371	49	256	136	3.67	95
	0-50	8.6	44	172	23	0.74	583	58	412	130	3.10	92
	50-100	22.6	45	181	86	0.83	1,290	66	928	123	3.05	89
32	B	2.8	21	119	0	0.84	221	—	—	130	—	—
	0-50	4.5	23	138	0	0.86	275	—	—	130	—	—
	50-100	11.6	28	152	0	0.95	592	—	—	127	—	—
34	B	1.6	17	68	0	0.60	121	22	129	145	4.50	107
	0-50	2.5	23	96	0	0.74	137	22	107	133	3.90	102
	50-100	7.5	25	122	11	0.74	240	27	201	126	3.49	97

Table 12 b. Infused amounts in the experiments reported in table 12 a. Legend as in table 11 b.

Case Hyp. nr.	Infusion rate			Case	Infusion rate		
	Water	Glucose	Insulin		Water	Glucose	Insulin
10	29.0	1.60	0	31	31.4	1.73	0.63
18	28.8	1.01	0	32	32.1	1.77	0
14	30.1	1.20	0.60	34	30.3	1.67	0.51

3. Calculation has further been made of the "average curve" for diuresis, sodium excretion, PAH clearance and inulin clearance, both for the normal subjects and for the 13 cases of arterial hypertension which with all probability can be labelled "essential". The curves were calculated according to the following method: Clearance and excretion values were calculated for the last 3 "basal" 10-minute periods before the commencement of the rapid infusion as well as for the 10 first 10-minute periods after this commencement. When the time for the beginning and the end of the clearance periods did not coincide with these time limits, the clearance value for the 10-minute period was calculated by a simple mathematical weighing. 13 periods were thus obtained for each experiment. They are fully comparable in time with corresponding periods from other experiments. For each period mean values and standard errors for each one of the two groups were calculated. It should be observed that mean values and standard errors do not retain their current significance here. The curves are to be considered as an illustration of the course of events, not as an exact description.

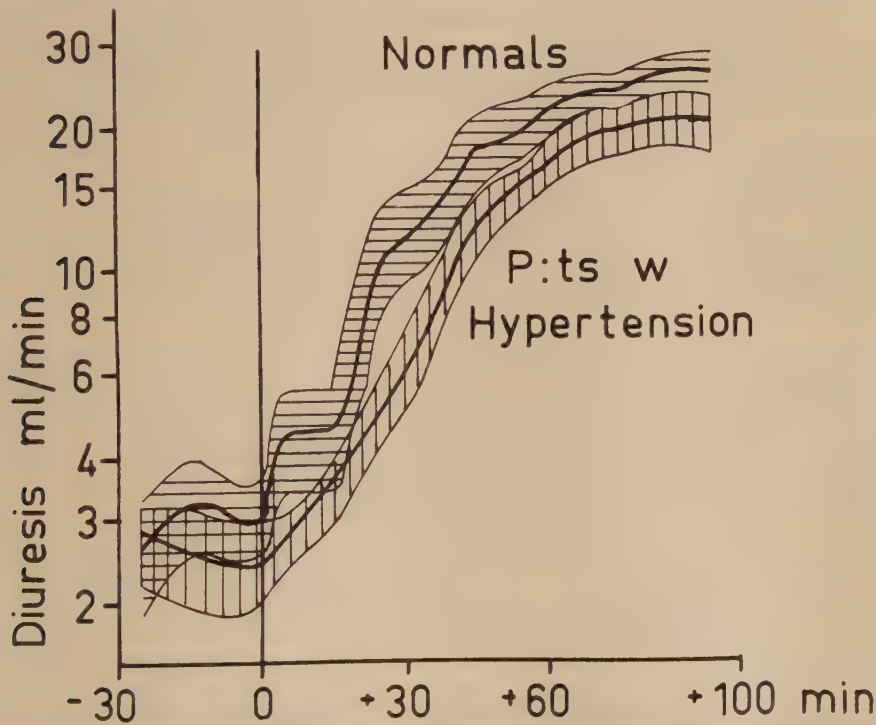


Fig. 1. The means of the diuresis in the experiments (reported in the tables 10 and 11 a) with a continuous rapid infusion given to normal subjects and to patients with "essential" arterial hypertension. The 0-line represents the start of the infusion. The diuresis was recalculated for 10-minute periods as described in text. The borders of the shaded areas correspond to the standard errors.

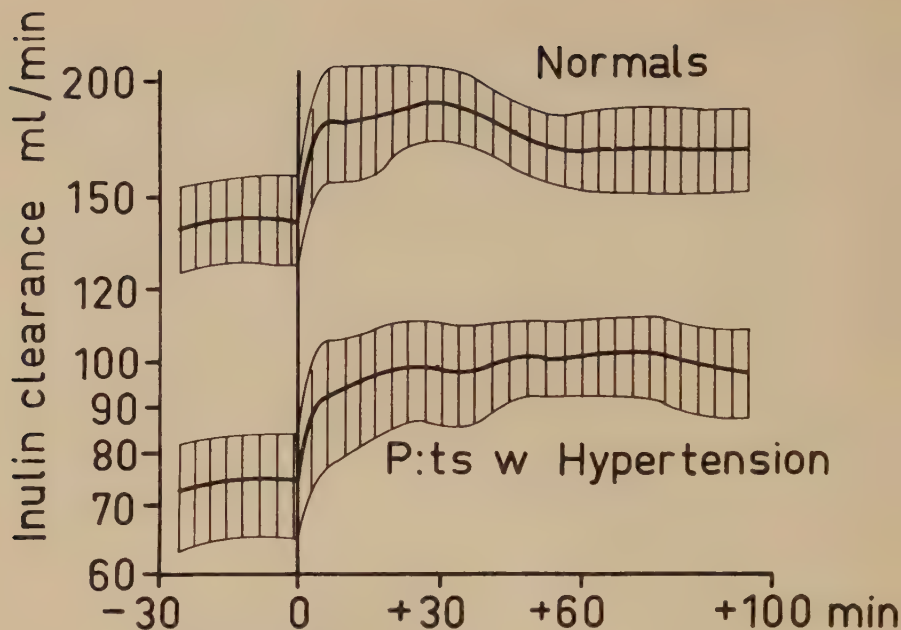


Fig. 2. The means of the inulin clearances registered in the same experiments as in fig. 1.
Legend as in fig. 1.

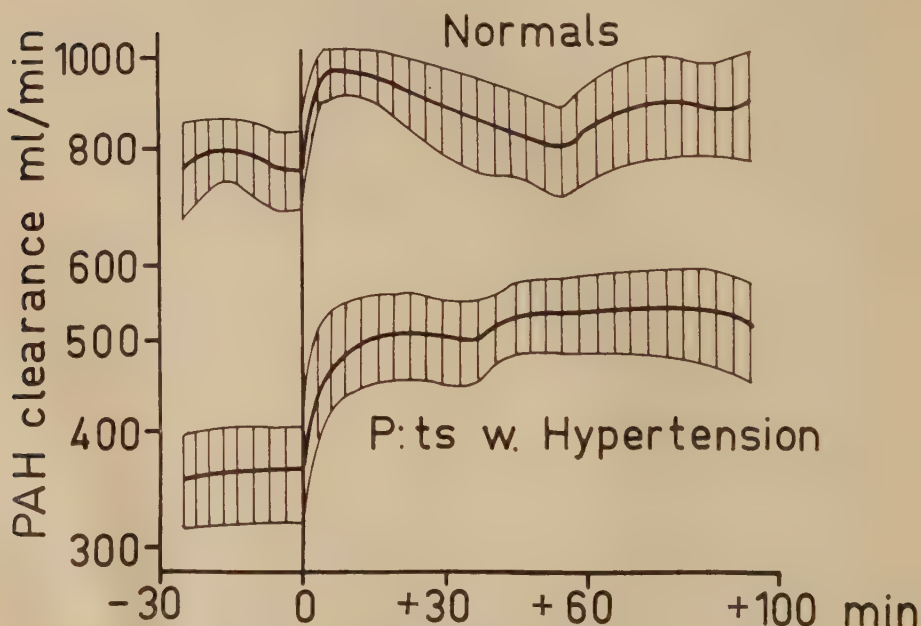


Fig. 3. The means of the PAH-clearances registered in the same experiments as in fig. 1.
Legend as in fig. 1.

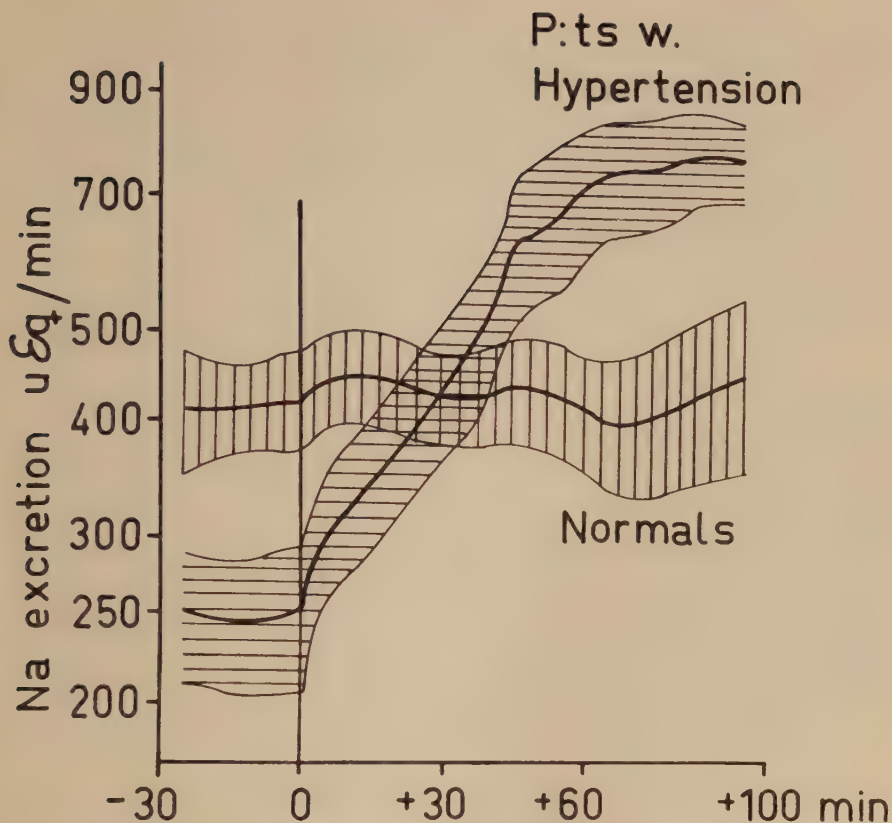


Fig. 4. The means of the sodium excretion values registered in the same experiments as in fig. 1. Legend as in fig. 1.

The results from the cases of arterial hypertension which are accounted for in Table 12 a have not been combined in "average curves" as it is thought that this material is not sufficiently uniform. Neither have the "average curves" for the potassium excretion been calculated for the material presented in Tables 10 and 11 a. As is shown in Table 11 a the changes in potassium excretion during rapid infusion were so heterogeneous in size and direction that an "average curve" would be meaningless.

4. In Table 14 the statistical probability is given that the changes presented in Tables 10, 11 a and 12 a constitute random values. Equally is given the size of the relative changes—and it is the P-values of the relative and not the absolute changes which are given in the table. There are two reasons for this: On the one hand Table 11 a and 12 a contain heterogeneous material—i.e. both advanced and early cases of disease; this in itself is a reason for using a relative basis of calculation. Secondly, clearance resp. excretion

values in Tables 10, 11 a and 12 a are not corrected to 1.73 m² BSA. Even though such correction may be suitable with regard to the clearance values, such a method of procedure cannot be used in connection with diuresis and electrolyte excretion values. For the sake of consistency the clearance values have not been corrected either. This gives a greater heterogeneity of the values which also means that more importance should be attached to the relative than to the absolute changes.

Table 13. Arithmetic means of the results reported in table 10, 11 a, and 12 a.

		Diuresis	Clearance		Urinary excretion				Plasma conc.	
			Inulin	PAH	Glucose	Creatinine	Na	K	Na	K
Cases in Table 10	B	3.2	144	791	0	1.37	424	106	132	3.68
	0—50	10.4	182	906	23	1.37	435	102	125	3.45
	50—100	23.6	169	860	83	1.23	425	61	124	3.09
Cases in Table 11	B	2.8	73	331	0	0.93	253	72	138	3.49
	0—50	6.2	94	478	22	1.11	457	83	134	2.98
	50—100	18.1	100	488	84	1.14	761	70	130	2.80
Cases in Table 12	B	2.2	38	199	0	0.80	234	54	136	3.98
	0—50	5.3	56	251	12	0.88	369	63	130	3.43
	50—100	16.7	60	248	51	0.95	760	65	126	3.12

Table 14. Means of the ratios calculated for each experiment between the results from the periods reported in tables 10, 11 a, and 12 a. *p* = the probability that the registered values do not deviate from 1.0.

	Normals			Cases of "essential" hypertension			Cases of non-essential hypertension		
	0'—50'	50'—100'	50'—100'	0'—50'	50'—100'	50'—100'	0'—50'	50'—100'	50'—100'
	Basal	Basal	0'—50'	Basal	Basal	0'—50'	Basal	Basal	0'—50'
Inulin clearance.	1.27	1.17	0.93	1.32	1.43	1.08	1.40	1.48	1.00
<i>p</i> <.....	1: 200	1: 100	1: 10	1: 200	1: 200	1: 20	1: 100	1: 40	1: 10
PAH clearance.	1.16	1.07	0.94	1.48	1.53	1.05	1.27	1.31	1.00
<i>p</i> <.....	1: 40	1: 6.7	1: 15	1: 200	1: 200	1: 6.7	1: 100	1: 40	1: 10
Creatinine.....	0.99	0.88	0.89	1.20	1.25	1.04	1.10	1.18	1.00
<i>p</i> <.....	1: 2.5	1: 40	1: 200	1: 200	1: 200	1: 5	1: 40	1: 200	1: 10
Na excretion...	1.06	1.02	0.98	1.99	4.62	2.04	1.49	3.22	2.00
<i>p</i> <.....	1: 3.33	1: 2.5	1: 2.22	1: 200	1: 100	1: 200	1: 40	1: 200	1: 10
K excretion....	0.99	0.59	0.59	1.34	1.11	0.90	1.15	1.25	1.00
<i>p</i> <.....	1: 2.22	1: 200	1: 200	1: 5	1: 4	1: 10	1: 10	1: 5	1: 10
Na serum conc..	0.95	0.94	0.99	0.97	0.94	0.97	0.96	0.92	0.90
<i>p</i> <.....	1: 200	1: 200	1: 4	1: 200	1: 200	1: 200	1: 100	1: 200	1: 20
K serum conc...	0.93	0.83	0.89	0.86	0.83	0.94	0.86	0.79	0.90
<i>p</i> <.....	1: 20	1: 200	1: 40	1: 200	1: 200	1: 40	1: 200	1: 200	1: 10
Filtration fraction.....	1.10	1.10	1.01	0.91	0.93	1.93	1.13	1.16	1.00
<i>p</i> <.....	1: 100	1: 10	1: 2.22	1: 40	1: 10	1: 5	1: 4	1: 6.67	1: 3

Table 15. Percentage renal extraction of PAH found by means of renal vein catheterization.
Time: start of infusion = 0.

Exp. nr								
B 3	Renal extraction of PAH. Time (minutes)	88.1 — 74	90.1 — 47	89.0 — 10	87.6 + 20	87.1 + 57	87.2 + 102	85.2 + 121
B 4	Renal extraction of PAH. Time (minutes)	94.8 — 58	93.4 — 45	92.8 — 9	90.8 + 22	90.1 + 39	89.5 + 93	87.0 + 123
Hyp. 4	Renal extraction of PAH. Time (minutes)	90.1 — 54	90.3 — 28	90.1 — 4	85.3 + 20	88.8 + 60	89.3 + 82	86.9 + 103
Hyp. 10	Renal extraction of PAH. Time (minutes)	87.5 — 118	88.5 — 94	87.3 — 17	74.9 + 19	62.7 + 49	76.7 + 80	78.9 + 93

In order to give a survey of the results registered in Tables 10, 11 a, and 12 a the means from each table have been calculated and are presented together in Table 13. It is obvious that the means from such a heterogeneous material as the hypertensive patients are of no value per se. The means are reported here only in order to demonstrate the differences in absolute values between the results from the different periods.

The percentage renal extraction of PAH was examined in four experiments by means of renal vein catheterization. Samples from a brachial artery and a renal vein were taken simultaneously several times during the experiments. The PAH concentration in plasma was fairly even and in these experiments it never exceeded 3 mg per 100 ml. The results are presented in Table 15.

II. The results of administration of a purine diuretic ("Oxyphyllin") during hydration

After the rapid infusion (described above) had continued for 100—120 minutes and the diuresis had become clearly stabilized 0.35 g theophyllin-1-aminopropanol-(2) (10 ml "Oxyphyllin" Astra) was given through the rubber tube and the vein needle in 5 experiments on normal subjects and in 5 experiments on hypertensives.

The results for the normal subjects are given in table 16, and for patients with arterial hypertension in table 17. In these tables only 3 clearance periods immediately preceding the Oxyphyllin injection, and those following it, have been included. The earlier periods when the diuresis was rising are of no interest in this connection. That the clearance and excretion experiments were followed for such a short time *after* the Oxyphyllin injection depends on two reasons: *firstly*, some of the subjects became indisposed and the experiments had to be discontinued; *secondly*, the object of the investigation was *not* to study the pharmacology of the Oxyphyllin as such, but to examine the reaction of the kidney to a practically instantaneous increase of the diuresis.

That experiments A₂, A₄, A₅, have not been included in table 10 is because no "basal" periods were determined in these cases. These experiments were started by the setting-in of the rapid infusion. Experiments A₆ (= B₃) and A₇ (= B₄) are, on the other hand, a direct continuation of the experiments registered in table 10. The same applies to the experiments 6, 10, 32, 14, registered in table 17. These are also included under the same numbers in

Table 16. Results from the experiments with a diuretic theophylline derivative (Oxyphyllin) on normal subjects. The experiments were started with a rapid infusion which continued during the whole experiment. The Oxyphyllin injection (represented by the horizontal line) was given when a "maximal" diuresis had been achieved during at least three periods.

$\frac{\text{Inulin}}{\text{creatinine}} = \text{inulin clearance ml/min. divided by creatinine excretion mg/min. Otherwise legend as in table 10.}$

Case nr	Min	Diuresis	Clearances		Urinary excretion				Urinary pH	Inulin Creatinine
			Inulin	PAH	Crea- tinine	Na	K	Cl		
A 1	18.5	29.4	133	659	1.17	767	46	465	6.74	114
	9.0	30.6	144	743	1.27	763	56	538	6.74	113
	7.0	30.3	133	741	1.22	818	52	633	6.89	109
	6.5	45.2	180	973	1.58	2,270	102	1,719	6.94	114
	8.0	44.3	151	783	1.33	2,990	121	2,323	7.16	114
	18.5	33.1	157	831	1.39	2,311	112	1,905	7.80	113
A 4	18.0	30.1	169	645	1.21	395	78	232	—	140
	10.5	30.2	150	621	1.13	393	66	260	—	133
	10.5	31.3	169	682	1.17	391	67	260	—	144
	9.5	47.1	206	743	1.45	1,366	141	923	—	142
	9.0	45.0	190	643	1.28	1,395	180	952	—	148
	24.5	42.5	188	623	1.30	1,182	145	797	—	145
A 5	17.0	21.4	166	661	1.45	321	54	210	6.35	115
	9.0	22.2	166	656	1.45	294	50	175	6.44	114
	9.0	21.4	156	670	1.37	268	53	159	6.41	114
	9.0	38.0	207	804	1.50	1,634	101	1,065	6.92	138
	19.0	34.4	190	709	1.42	1,523	101	1,063	6.92	134
	18.0	26.2	164	630	1.26	1,305	91	944	7.01	133
A 6 (= B 3)	23.0	31.2	166	801	1.11	397	67	329	6.25	150
	22.0	34.5	158	834	1.09	466	69	379	6.30	145
	10.5	38.5	186	969	1.30	500	79	402	6.21	143
	8.5	52.8	357	1,002	1.47	1,083	110	1,377	6.85	243
A 7 (= B 4)	6.0	41.5	347	911	1.27	1,183	98	1,022	7.03	273
	19.0	18.1	138	834	1.35	609	79	421	6.18	102
	17.5	19.5	146	966	1.48	573	61	440	6.15	99
	16.5	21.0	153	1,090	1.48	556	53	375	6.06	103
	5.0	28.8	200	1,498	1.77	821	81	547	7.01	113
	9.5	31.1	177	1,233	1.61	1,024	73	730	7.13	110

Table 17. Results from the experiments with a diuretic theophylline derivative on patients with arterial hypertension during rapid infusion. Legend as in table 16.

Case nr	Min	Diuresis	Clearances		Urinary Excretion				Inulin
			Inulin	PAH	Creatinine	Na	K	Cl	Creatinine
Hyp 6	12.0	17.2	73	226	1.07	694	96	—	68
	8.5	17.7	67	248	1.08	733	92	—	62
	12.5	18.3	66	261	1.03	821	88	—	64
	5.5	26.2	88	327	1.41	1,546	121	—	62
	13.0	23.5	69	268	1.10	1,669	113	—	63
	10.0	15.5	80	295	1.22	1,643	81	—	66
Hyp 10	15.0	30.2	77	288	1.06	1,793	133	1,647	73
	18.0	31.2	70	289	1.02	1,971	126	1,859	69
	15.0	29.7	74	282	1.03	1,617	125	1,554	72
	9.0	31.2	78	300	1.06	1,893	144	1,703	74
	9.0	23.6	65	272	0.92	1,767	141	1,510	71
Hyp 17	10.0	3.1	119	292	1.22	434	54	372	98
	14.0	3.7	101	266	1.02	529	69	459	99
	16.5	3.0	88	252	0.86	460	64	399	102
	5.5	5.3	149	439	1.28	804	79	699	116
	19.5	0.5	16	59	0.17	68	14	70	94
Hyp 32	12.5	9.3	22	124	0.84	464	—	—	26
	12.5	13.6	30	164	1.11	707	—	—	27
	11.0	13.5	29	156	1.08	686	—	—	27
	8.5	25.2	53	274	1.91	1,309	—	—	28
	11.0	21.8	40	196	1.36	1,353	—	—	29
	11.0	18.5	33	168	1.17	1,033	—	—	28
Hyp 14	13.0	24.2	141	462	1.22	386	53	—	116
	12.5	25.7	130	399	1.33	424	53	—	98
	11.5	25.4	130	391	1.25	419	47	—	104
	11.0	41.3	309	431	1.51	1,620	95	—	205
	12.0	36.7	266	384	1.33	1,172	83	—	200

tables 11 a and 12 a. Case 17 had only received the rapid infusion during 88 minutes. As the diuresis was low, despite the infusion, and showed no sign of rising, 10 ml Oxyphyllin was given afterwards. Soon after the injection the patient had a short "black out". It is possibly inconsequential that this experiment was included. It may, nevertheless, be of certain interest, although of a somewhat different kind than that attached to the other experiments.

III. Peroral supply of beer resp. water

Each one of the patients with arterial hypertension on whom experiments with peroral fluid supply were undertaken was requested to drink approximately

2 litres of water during two hours, resp. 2 litres of beer during two hours, in two separate experiments. The experiments were begun—after a fast—between 11 and 12 o'clock in the morning. Each experiment was registered separately. The patients were encouraged to empty their bladders as often as possible. During the individual experiments the patient was never encouraged to attempt emptying the bladder at any given time. Such imperative measures often seem to result in an inability to void at the given point of time. For this reason the actual number of voidings in the two experiments were different in one and the same individual; the total time taken up by the voiding periods after the consumption of beer and water had started, was, on the other hand, almost identical.

Even under these conditions it was difficult to obtain relatively complete voidings of the bladder. This is shown by a number of indirect indications. During earlier research (Ek and Josephson 1953 a) concerning peroral fluid supply to normal subjects the diuresis followed with respect to time a bell-shaped curve (resembling a symmetrical, normal frequency distribution curve). In certain subjects of experiment this curve was markedly "jumpy". If the average creatinine excretion during the experiment was determined in mg/min. and this sum was divided by the creatinine content of the separate portion of urine (mg/ml) a "volume sum" was obtained which was closely similar to the measured diuresis. If these "creatinine numbers" were plotted as a function of time the curve became much more even than when the directly measured diuresis values were used. No consistent change in the creatinine excretion could be observed during the experiment.

Tables 18 a—23 b. Results from the experiments when patients with arterial hypertension drank 2 lit. of water resp. beer in 2 hours. The columns to the left of the double line represent the periods before the start of the drinking. Diuresis in ml/min. sodium and chloride in μ Eq/min. Calculation of diuresis and sodium and chloride excretion described in text.

Table 18 a. Hyp. 3.

Water										
Diuresis....	1.5	1.5	1.9	1.8	5.2	12.5	14.8	16.8	18.3	17.8
Sodium....	284	323	319	374	343	442	549	542	611	650
Chloride....	317	279	371	312	208	387	435	458	474	513
Minutes....	36	29	24	22	21	16	15	12	10	18

Table 18 b.

Beer							
Diuresis.....	2.7	6.2	17.8	17.5	18.8	19.6	18.9
Sodium.....	77	253	326	333	258	317	413
Chloride.....	60	190	280	298	260	298	378
Minutes.....	29	48	18	11	12	13	11

Table 19 a. Hyp. 21.

Water						
Diuresis.....	1.0	0.9	2.5	5.8	7.5	7.6
Sodium.....	89	93	82	82	110	118
Chloride.....	128	116	110	154	136	172
Minutes.....	33	38	53	25	20	19

Table 19 b.

Beer										
Diuresis....	0.9	2.3	4.9	7.0	6.4	10.4	10.8	10.8	11.2	12.1
Sodium....	88	72	109	146	130	218	233	233	236	248
Chloride....	104	80	112	148	121	198	211	211	202	214
Minutes....	31	36.5	24.5	16	13.5	10	10.5	12.5	11.5	16.0

Table 20 a. Hyp. 41.

Water									
Diuresis.....	3.6	4.8	4.3	4.2	4.7	10.9	11.6	10.9	
Sodium.....	591	717	673	582	427	554	378	284	
Chloride.....	473	561	533	454	378	416	282	206	
Minutes.....	47	38	19	13	19	17	10	10	

Table 20 b.

Beer										
Diuresis....	0.4	0.8	1.2	2.0	3.1	1.7	2.4	2.4	3.2	3.0
Sodium....	25	56	86	76	85	74	81	59	60	42
Chloride....	10	50	91	64	111	43	83	44	61	94
Minutes....	236	41	30	24	23	19	12	13	17	22

Table 21 a. Hyp. 42.

Water									
Diuresis.....	1.0	3.2	2.9	9.6	12.6	17.9	14.0	15.0	
Sodium.....	138	117	391	284	253	607	302	375	
Chloride.....	102	130	183	191	163	413	217	237	
Minutes.....	194	66	28	21	17	17	27	13	

Table 21 b.

Beer										
Diuresis....	0.4	0.9	4.2	11.0	12.9	12.6	20.6	19.7	19.6	
Sodium....	100	74	433	626	356	123	515	404	471	
Chloride....	55	88	384	417	269	94	402	311	304	
Minutes....	129	50	25	14	16	15	15	15	15	

Table 22 a. Hyp. 43

<i>Water</i>						
Diuresis.....	0.6	0.6	2.7	6.9	6.5	7.8
Sodium.....	34	40	90	121	88	70
Chloride.....	37	44	75	93	63	53
Minutes.....	114	66	44	30	35	27

Table 22 b.

<i>Beer</i>						
Diuresis.....	0.6	0.5	1.2	2.9	7.0	8.5
Sodium.....	25	20	72	98	132	115
Chloride.....	28	22	65	89	111	112
Minutes.....	132	46	45	34	28	34

Table 23 a. Hyp. 44.

<i>Water</i>							
Diuresis.....	0.6	0.5	0.6	0.8	2.4	6.0	8.1
Sodium.....	98	78	111	130	111	169	202
Chloride.....	113	84	113	129	115	140	185
Minutes.....	26	40	26	22	27	29	15

Table 23 b.

<i>Beer</i>									
Diuresis.....	1.1	1.1	1.5	3.6	9.0	12.9	14.8	14.4	13.3
Sodium.....	184	221	261	251	305	318	280	237	190
Chloride.....	179	191	222	239	305	170	142	137	145
Minutes.....	21	25	35	18	19	10	10	10	10

In tables 18 a to 23 b the presented diuresis was calculated in this way. Sodium and chloride are calculated as a product of electrolyte concentration and the thus calculated diuresis. The irregularities in water and electrolyte excretion which appear in these tables probably do not, therefore, depend on voiding errors but on other phenomena which will be discussed later.

DISCUSSION OF METHODS

For purely practical reasons, before the general discussion, a number of methodical and other similar problems will be discussed here.

I. Can the different analysed elements affect each other's chemical determinations so that apparent changes can arise?

The determination of Na, K and Cl is not affected by the presence of glucose, inulin, para-amino-hippuric acid (PAH) and creatinine. Except for the ordinary errors of the flame-photometric methods the determination of electrolyte excretion values can scarcely have been affected by other elements than these. According to general experience, inulin, PAH and creatinine determinations do not influence each other. The question remains, however, as to the degree in which glucose may affect determination of these three elements. With regard to inulin, glucose was fermented both in urine and plasma before the determinations.

As regards urine-creatinine, the question is answered in table 2. Finally, as regards PAH it is indisputable that PAH and glucose may form a combination which cannot be determined by ordinary PAH methods of analysis (Baldwin, Schreiner, Breed, Wesson and Maxwell 1950). This combination is formed slowly (tab. 3, ch. 3) and should, during the actual conditions of experiment, only constitute a negligible part of the infused PAH quantity. The influence of this combination on PAH clearance values is not clear. There is a possibility, that it may decrease the PAH transport by competition. In such case, this might at least contribute to the recognized reduction of the renal extraction of PAH. As has been pointed out earlier, this would mean that the increase in RPF shown here, would be still greater than that which corresponds to the increase in PAH clearance.

The above named PAH-glucose combination does not under normal conditions (slow infusion) increase PAH clearance. On the contrary PAH clearance decreases, according to Baldwin, Schreiner, Breed, Wesson and Maxwell (1950) while RPF remains practically constant.

In addition, two things should be emphasized: firstly, that parallelism between PAH clearance and inulin clearance is good, and secondly that in one case (Hyp. 11) PAH was substituted by Umbradil (Diodrast) whereupon RPF was followed by means of kidney vein catheterization. During the rapid infusion the increase in RPF was of the same size as the PAH clearance increase in the other experiments. As the diodrast concentration in this case was above the "depression limit", and increased slowly, it was not possible to determine whether the glucose infusion affected the renal extraction of diodrast.

To summarize the above discussion, it may be said that there is nothing to suggest that the results obtained have been affected to any mentionable degree by chemical interference.

II. Can the results be explained altogether or in part by "unintended" physiological effects?

A. *To what degree does psychical irritation, pain and discomfort influence the results?*

It is a well known fact that pain, psychical irritation and discomfort affect considerably the various functions of the kidney, such as filtration rate, RPF and diuresis. For a survey of this problem see Smith (1951), Wolf (1950), Bykow (1953). In the present paper attempts have been made to avoid such disturbances as much as possible, although this has not entirely prevented their development in certain cases.

During *the experiments with rapid infusion* the subjects sometimes complained of tenderness round the artery cannula. This can usually be eliminated by further infiltration anaesthesia. The vein needle and the vein catheter seldom caused any trouble. What most of the subjects found irritating was the bladder catheter and emptyings of the bladder. During the first 100 minutes of the rapid infusion, indisposition occurred in exceptional cases only. Two experiments during which vomiting and shivering occurred were omitted. In a few cases vomiting and indisposition followed after the experiments.

The main point is, however, that when the rapid infusion was begun this did not cause any further pain or discomfort, for the reason that the infusion

went into the already indwelling vein needle. Neither could it be observed that commencement of the rapid infusion gave rise to anxiety or any other psychical irritation.

It is obvious that the subjects of experiment cannot be considered to be in a completely "basal" condition during the entire period of experiment, *inter alia* because every clearance experiment must necessarily involve a certain mental and physical discomfort. It is, however, difficult to see how such factors can have been changed to any degree during the experiment—and it is the quick change in the clearance values at the commencement of the rapid infusion which is of most interest in this investigation. Equally, these factors can scarcely account for the differences in electrolyte excretion between normals and hypertensives which are demonstrated.

Concerning the *peroral fluid loading experiments*, circumstances are to some degree different; the only discomfort which was felt by a few of the subjects during any of these experiments was nausea.

Different people—both normal and hypertensive—show a greatly varying reaction to fluid consumption. When fluid consumption causes indisposition, the renal blood flow, filtration, diuresis and electrolyte excretion seem to decrease. After a number of preliminary experiments it was found that the largest peroral standard dose which could be used without causing discomfort was 2 litres per 2 hours. But when this dose was given simultaneously with the carrying-out of an ordinary clearance examination (with an artery cannula, vein needle, bladder catheter, in a recumbent position) extreme discomfort was none the less experienced in three consecutive cases, and in connection with this the disturbances in kidney function which are mentioned above occurred. This was interpreted as the result of some kind of summation of gastrointestinal irritations (dumping syndrome?) as well as the ordinary irritations resulting from a clearance examination. Thus the fluid loading experiments had to be carried through without clearance examination, and I was therefore obliged to confine myself to following the electrolyte excretion only. Some degree of discomfort appears still to have been felt under these experimental conditions, although not nearly so intense as during the clearance experiments. This varying reaction to the same peroral loading may possibly depend on the fact that the clearance experiments were carried out with the subject in a recumbent position, while during the later experiments the subjects sat upright.

B. The "washing-out" effect

When diuresis increases rapidly the diluted urine rinses away the earlier, more concentrated urine which is already present in the urinary tracts. The first

urine portion during high diuresis will thus be more concentrated when voided than when it entered the pelvis. In this way a "false" increase in the excretion of solutes may appear. A factor which to some degree counteracts this increase is that the renal dead space (in which the bladder volume is not included) appears to increase with the increase of the diuresis. An instructive analysis of these problems has been published by Bojesen (1949). The question remains as to how far the effects of "washing-out" can explain the clearance increase appearing with short latency time after the start of the rapid infusion. It is probable that the increase is to some extent due to the "washing-out" effect. With normals (see fig. 4) the average initial increase of sodium excretion after the commencement of the rapid infusion was 5 per cent. The increase of PAH clearance, on the other hand, was about 27 per cent. Assuming that the rapid infusion does not affect the sodium excretion—which is inferred by the appearance of the curve (see fig. 4)—the washing-out effect should therefore give a "false" excretion increase of 5 per cent, and the actual PAH clearance increase should be 21 per cent. In the hypertensives, on the other hand the sodium excretion cannot be used as reference for clearance increase since their sodium excretion rises during the rapid infusion. In 12 of the 19 investigated cases with arterial hypertension the PAH clearance increased more than the diuresis during the first period after the commencement of the rapid infusion. On an average PAH clearance increase for all 19 cases was 19 per cent higher than the diuresis increase. There is nothing to support the assumption that the washing-out effect in hypertensives (with the possible exception of pyelo-nephritis cases) is greater than in normals. The percentage increase of the PAH clearance was, however, very much larger in cases of hypertension than in normals. (See fig. 3.) It is, therefore, probable that the share of the washing-out effect in the clearance increase is considerably smaller in cases of hypertension than in normals.

C. Can changed renal extraction of PAH affect interpretation of the PAH clearance results?

The renal extraction of PAH in hypertensives appears to be normal or almost normal (c. 90 per cent) provided that PAH clearance has not sunk as low or lower than c. 300 ml (Reubi and Schroeder 1949, Cargill 1949). In the present investigation the renal extraction of PAH sank during the rapid infusion in 2 normals and 2 cases of hypertension. (See tab. 15.) This is a strong indication that the registered increase in PAH clearance corresponded to a still greater increase of the RPF. As the extraction was only determined in 4 cases and as the decrease of the renal extraction was not equal in all the experiments it was not possible to correct the results of the PAH clearance to apply to

the RPF. This means that the changes in "filtration fraction" are very dubious. For this reason they will not be further discussed.

D. *Can the registered changes in electrolyte excretion have been affected by the diurnal rhythm?*

It has long been well known that chloride and sodium excretion is normally low during the night, but increases in the morning and sinks again towards evening. It is also well known that certain diseases such as nephritis and heart failure often show abnormal diurnal variations as regards electrolyte excretion. To the best of my knowledge no investigation has been published on the 24-hour curve of patients with compensated hypertension. It should, however, be observed that in the present investigation the rapid infusion was started at varying points of time during the 24 hours (between 10.43 and 12.46) and that the sodium excretion first began to increase after the commencement of the infusion. In addition, the sodium excretion figures from the three 10-minute periods before the commencement of the experiments on hypertensives remained very steadily on the average curve. After 30 minutes of infusion the sodium excretion had, on the other hand, already risen by 64 per cent. It is, therefore, unlikely that electrolyte excretion during the experiment was affected to any marked degree by the diurnal variations.

In normals the excretion of sodium and chloride changed only a little during the fluid infusion and the diurnal variations can scarcely have been of any influence as all the experiments were carried out about noon.

GENERAL DISCUSSION

I. Experiments with rapid infusion and peroral fluid loading

A. General Remarks

1. *Appraisal of the degree of hydration*

The fluid quantity of the rapid intravenous infusion should distribute itself throughout the fluid compartments of the organism. However, the continuous supply of fluid to the circulating blood volume, the actively changing diuresis, and the "backward flow" of the fluid to the gastro-intestinal tract¹, all contribute in making it extremely doubtful whether any "steady state" ever occurs between the various fluid compartments of the body during the experiments. As a reasonably accurate measurement of these compartments presumes this "steady state", no attempts have been made to measure the different fluid compartments. The simple balancing calculation "injected quantity $\div$ excreted urine" could be used as a rough measurement of "the degree of hydration" *if* the above-mentioned flow to the gastro-intestinal tract did not occur, and *if* it were possible to assume that all subjects, both normal and hypertensive, have a fully comparable degree of hydration at the beginning of the experiments. One cannot, however, assume that such was the case. For practical reasons it was impossible to standardize the diet or the fluid supply during the days previous to the experiment.²

It should further be pointed out that the reaction of a given subject of experiment to fluid supply does not seem to depend entirely on the quantity of salt resp. water already in his fluid compartments at the beginning of the experiment. Ladd (1950) has shown that if a subject of experiment has received

¹ This "backward flow" must be anticipated as subjects of experiment who have not received water perorally for over 12 hours can experience watery attacks of vomiting, especially after the taking of oxyphyllin.

² The diet of the patients with arterial hypertension contained 6-8 g NaCl a day:

2 litres of water perorally 7 to 14 hours before receiving an infusion of sodium chloride he will react to the infusion with a rapid, high diuresis and hemo-concentration. Should, however, the period of time between the peroral loading and the sodium chloride infusion be over 14 or under 7 hours, the effect of the latter will not be nearly so great. It is not known whether this remarkable phenomenon can be of significance for the way in which subjects of experiment react to the intravenous supply of glucose.

2. The Effect of Glucose

The purpose of the intravenous supply of isotonic or hypotonic glucose solution, with or without the addition of insulin, was to achieve something which with as few reservations as possible could be called "pure" hydration.

In theory, distilled water is obviously the most suitable infusion fluid for "pure" hydration. During preliminary experiments which are at present in progress, it has been found that 25—30 ml distilled water per minute can be given intravenously without causing hemolysis if the infusion is given centrally in the vein system (in vena cava or right auricle) via a catheter. There are, however, strong theoretical reasons for believing that distilled water given in this way is distributed unevenly in the interstitial fluid compartments; it is probable that the lungs in particular initially receive more water interstitially than the rest of the body. As this appears to involve special effects, and because the material examined is still too small, the results of these experiments will not be considered here.

During the rapid infusion the subjects of experiment received a quantity of glucose which varied between 630 and 1,720 mg/min. Glucosuria was in most cases negligible. In those normal subjects where oxygen consumption was followed, the latter showed little or no increase during the rapid infusion.

It has long been known that the intravenous supply of glucose reduces the potassium concentration of the plasma. In the present experiments (see tables 10, 11 and 12) the potassium concentration in plasma decreased more than the sodium. This means that the experimental conditions were scarcely suited to the study of potassium metabolism during pure hydration. It will be considered later how far glucose as such can have affected the results even in other respects.

B. Clearance changes during rapid infusion

As is shown by figs 2 and 3 both the PAH and the inulin clearance increased immediately after the commencement of the rapid infusion. In most cases the first period after the commencement of the infusion was approximately 20 minutes. The picture given by figs 2 and 3 can, therefore, be misleading;

the lag time between the commencement of the infusion and the increase in the clearance cannot be directly interpreted from the figures. It can, however, be calculated which logical sequence—as regards clearance increase—a certain, presumed lag time would give. Suppose the lag time to be 10 minutes. The increase of clearance values which is represented in figs 2 and 3 as occurring between 0 and 20 minutes must then be wholly assigned to the period of time between 10 and 20 minutes. For normals this would mean that the average PAH clearance during the rapid infusion increased by over 50 per cent. For the 13 cases of arterial hypertension represented in table 11 a the corresponding figure would be 67 per cent. These figures for the increase of the clearance values become so high that it would be more reasonable to suppose a shorter lag time than 10 minutes—the initial increase would then be proportionately lower.

I have attempted to show earlier that “the washing-out effect” cannot substantially have influenced the measurement of the initial clearance increase. One is thus forced to the conclusion that both in normals and in cases with arterial hypertension the PAH and inulin clearances show a noticeable increase after at most 10 minutes of rapid infusion, and probably even earlier.

In the 25 experiments with rapid infusion the subjects of experiment received during the first 10 minutes exactly 250 ml fluid average netto (infused quantity $\div$ diuresis). The corresponding figure for glucose given was 12.5 g. Neither of these quantities are in themselves so large that, according to current experience, they usually give such a fundamental physiological effect as an increase of over 50 per cent of the RPF. (If one reckons with a shorter lag time one will obtain a lesser increase in the clearance values, but at the same time it will be necessary to count with smaller—although active—infused quantities.)

The conclusion is readily drawn that it is the speed of the infusion which is the determining factor rather than the infused quantities in themselves, the speed of the expansion of some fluid compartment rather than the actual size of such an expansion.

It is of interest in this connection that Brod, Fejfarová and Chytil (1954) have investigated hemodynamic and functional changes in the kidney during the infusion of glucose. Their material consisted of normals and subjects of experiment with various diseases which usually give rise to kidney damage. 3 were cases of essential hypertension. The method of investigation was entirely different from that used in this paper. After “basal” periods 5 ml 20 per cent glucose was given per minute (the further experimental methods are of no interest in this connection). They found that PAH and inulin clearances increased initially even though the diuresis simultaneously decreased

and despite the fact that the glucose content of the blood had not had time to rise to any degree worth mentioning and that glucosuria had not yet occurred. They interpreted the phenomenon as an effect of water shift from the cells into the extracellular fluid, and that the expansion of the extracellular water compartment caused the increase of the clearances through some form of reflex. The explanation seems probable and corresponds closely to the working hypothesis on which the present paper is based.

Schmitz (1932) demonstrated that the infusion of isotonic saline greatly increased the glomerular filtration rate in dogs. This has subsequently often been confirmed, and has been shown to be valid for PAH clearance too. These clearance increases can best be interpreted as an effect of the expansion of the extracellular fluid compartments. The same reaction as in dogs (and rats) has been obtained in children (Dean and McCance 1949). But according to Smith's (1951) review of the problem—which has been followed—rapid infusion of physiological saline does not produce any certain or consistent increase of inulin or PAH clearance in the adult man. This would appear to contradict the hypothesis that an expansion of the extracellular fluid compartment may be the reason for increased clearance of the above-named substances. The contradiction may be explainable if by expansion of the extracellular fluid compartment is meant not only the increase in volume, but also the changes directly consequent on this. These changes are not necessarily the same on injection of isotonic glucose as on injection of isotonic saline, given at the same rate of infusion.

Up to the present, normal material and material with arterial hypertension have been treated jointly, as they both react to rapid infusion in a basically similar manner, *i.e.* with an acute increase of the PAH and inulin clearance. There were however, certain differences in the clearance reaction to rapid infusion in the examined material of both these groups. While in the case of normals the second 50-minute period during the infusion was lower than the first both as regards the inulin and the PAH clearances, the situation in cases with arterial hypertension appeared to be the opposite.

The *relative* increase (compared with the basal values) of PAH and inulin clearance was greater in patients with hypertension than in normals in the present investigation. This applies both to the first and to the second 50-minutes period.¹

¹ It has been tested whether »the normals» and »the patients with arterial hypertension» can be regarded as belonging to the same group with respect to the *relative* increase of PAH clearance. The probability that this is the case is for the first infusion period of 50 minutes 1:20, for the second 1:200.

Analogous values for inulin clearance is 1:4 respectively 1:40.

If, on the other hand, the clearance increase is measured in absolute figures, in ml per minute, (see table 13) the difference between normals and hypertensives is not so striking. It is obvious that in the material with arterial hypertension there were cases with gravely diseased kidneys; in such cases one cannot expect to find any greater or positive increase of the clearance values. If, however, all cases whose "basal" PAH clearance was under 300 were to be removed from tables 11 a and 12 a, 9 cases would remain. In these cases the PAH clearance increased 163 ml/min. (the period 50—100 minutes after the commencement of the rapid infusion compared with the "basal" period). In the 6 normal subjects the corresponding figure is only 69 ml/min. The difference between these two increases is, however, not statistically confirmed ($p = 1:6.6$). It should be pointed out that both these materials are very small for the making of such a comparison.

It is of great interest to know whether patients with arterial hypertension can be "normalized", *i.e.* can reach clearance values which are within the normal range. Bucht (1951) examined 27 men and 23 women in this laboratory, all of them normals according to all criteria. Corrected to 1.73 m² BSA the average mean for PAH clearance was exactly the same for both men and women, *i.e.* 557 ml/min. The frequency distribution curve is so skewed that an ordinary calculation of the standard deviation has not much significance. Only one of his subjects had a PAH clearance lower than 350 ml/min. I have therefore chosen this figure as the lower normal limit. Analogously calculated, the average mean for inulin clearance in normals is 120 ml/min. and the lower limit 80 ml/min. In the cases of arterial hypertension represented in tables 11 a and 12 a, 11 cases exceeded this lower limit for PAH clearance during the rapid infusion. 5 cases exceeded the average mean for normals. The corresponding figures for inulin clearance are 10 resp. 5 cases.

As has been pointed out earlier, and illustrated subsequently by the above, the clearance changes which often occurred in patients with hypertension were partly or entirely reversible. One could expect that patients with obvious, pathologically verified kidney disease (as in case 10/18) and with greatly lowered clearance values would not react with mentionable clearance changes. Even here, however, the kidney seems to retain a strong capacity to react to suitable stimuli by increased RPF and "filtration rate" (inulin clearance).

It seems reasonable to assume that the kidney arterioli in cases of hypertension have an abnormally high tonus, and that this can be dissipated separately while the other vessels in the body remain in their pathologically high tonus. This is shown by the fact, *inter alia*, that certain drugs (digitalis or a mixture of apresoline and noradrenaline) can considerably increase the RPF despite the fact that the changes in the blood pressure resp. cardiac output

are small. Even during the rapid infusion the blood pressure remained basically unchanged.¹

It is probable that the increase of inulin clearance which was observed is a result of hemodynamic changes in the kidney—in such case a dilatation of the afferent arterioli is to be expected. That the increase in the rate of filtration is dependent on a reduction of the colloid osmotic pressure of the plasma is less probable—chiefly because the increase of inulin clearance occurs as soon as even a small quantity has been injected.

The tentative hypothesis drawn from the above argumentation may be summarized as follows: The rapid infusion causes a quick expansion of the extracellular fluid compartment. This volume expansion or some phenomenon directly connected thereto provokes through some reflex a dilatation of the kidney vessels. This dilatation causes hemodynamic changes of such a nature that the inulin clearance (filtration) also increases.

It should be particularly emphasized that the findings which have been discussed in this paper could be theoretically explained if one assumes that the initial, decisive factor was not an expansion of the extracellular fluid compartment but a rapid rise of the blood glucose level.

The indications which support an assumption that the supply of water, not of glucose, was the decisive factor in my experiments are at first hand as follows:

a) The subjects who had received insulin in the infusion fluid showed an early high, concentration of glucose in the blood. This concentration decreased during the latter part of the experiment. The PAH and inulin clearances showed at the same time a further increase.

b) Clearance experiments on man with different forms of glucose loading have been carried out in a large number of investigations by many authors. If the increased glucose concentration as such is the cause of an increase in the PAH and inulin clearances of the order of magnitude reported here, it is probable that this increase had been observed earlier.

c) In a series of investigations where cases of mitral stenosis were examined by the same technique as that used in the present study (Werkö, Ek, Bucht and Varnauskas 1954) the kidneys reacted in all respects analogously with the hypertensive cases. In one of these mitral stenosis cases the method was changed so that instead of glucose solution a hypotonic solution of different amino acids (Aminosol) was administered. (This case was not reported in

¹ On the other hand the blood pressure in a large number of cases sank noticeably after the *conclusion* of the glucose infusion. This depression has lasted from 12—36 hours. As the experiments published in this paper have not been intended for the study of this problem, the question of the above-mentioned fall in the blood pressure will not be further considered.

the above-named publication.) In this experiment too, as well as in the others, a rapidly occurring increase in the PAH and inulin clearances was obtained.

It must be admitted, however, that these indications do not completely exclude the possibility, that the results are due to the administered glucose.

C. The Excretion of Water and Strong Electrolytes

1. The normal diuresis response

Shortly after the rapid infusion was started in a normal subject the diuresis began to rise in an S-shaped curve (fig. 1) and gradually stabilized itself at a "maximum level". This "maximum level" was reached after 70—90 minutes of rapid infusion. Between 50 and 100 minutes the diuresis in normals was between 19 and 32 ml/min. when about 25 ml/min. were infused.

2. The diuresis response in hypertensives

In 9 cases among the 19 experiments on patients with arterial hypertension which are reported in tables 11 a and 12 a a diuresis response occurred which did not diverge from that of the normal subjects. In 10 cases the diuresis was lower during the time between 50 and 100 minutes after the commencement of the infusion than the lowest value in the normals. To these should be added case 17 (reported under the Oxyphyllin experiments) in which the diuresis was so poor that it was not considered suitable to continue the infusion for 100 minutes. Among the patients who received peroral water loading there also occurred cases which responded with poor diuresis.

The correlation between the diuresis response on rapid fluid supply and the conventional renal function tests appears—in patients with arterial hypertension—to be non-existent or only negligible. (Compare for ex. case 4, table 11, with case 31, table 12.) I will return to the diuresis variations and "diuresis roof" in the discussion of the Oxyphyllin experiments.

Ellis and Grollman (1949) found in the urine of patients with hypertension an anti-diuretic substance (11 cases of 15) which was not, on the other hand, found in normal subjects under the same conditions. An interpretation of such findings is, however, problematic. In particular the slight, frequently-found proteinuria makes it reasonable to wonder whether in Ellis' and Grollman's experiments it may have been as much a question of a pathological "passing through" the kidney of an antidiuretic factor as an increased blood concentration of the said factor. In order to solve the problem of the pathological occurrence of anti-diuretic substances in patients with hypertension, an assay of the blood of such patients during hydration would appear inevitable.

3. Excretion of sodium

In the case of *normal subjects* the sodium excretion was remarkably steady during the entire experiment. The rapid infusion with its subsequent strongly increased diuresis did not appear to affect the excretion of sodium (and chloride). This is shown by figs 4, 5 and 7.

Patients with arterial hypertension showed themselves to be entirely different in this respect. Figs 4, 6 and 7 clearly indicate that in hypertensives—in contrast to normals—there exists a definite “companionship” between water and sodium in the urine. To express this “companionship” in one figure is difficult. The method represented in fig. 7 has been chosen as the most objec-

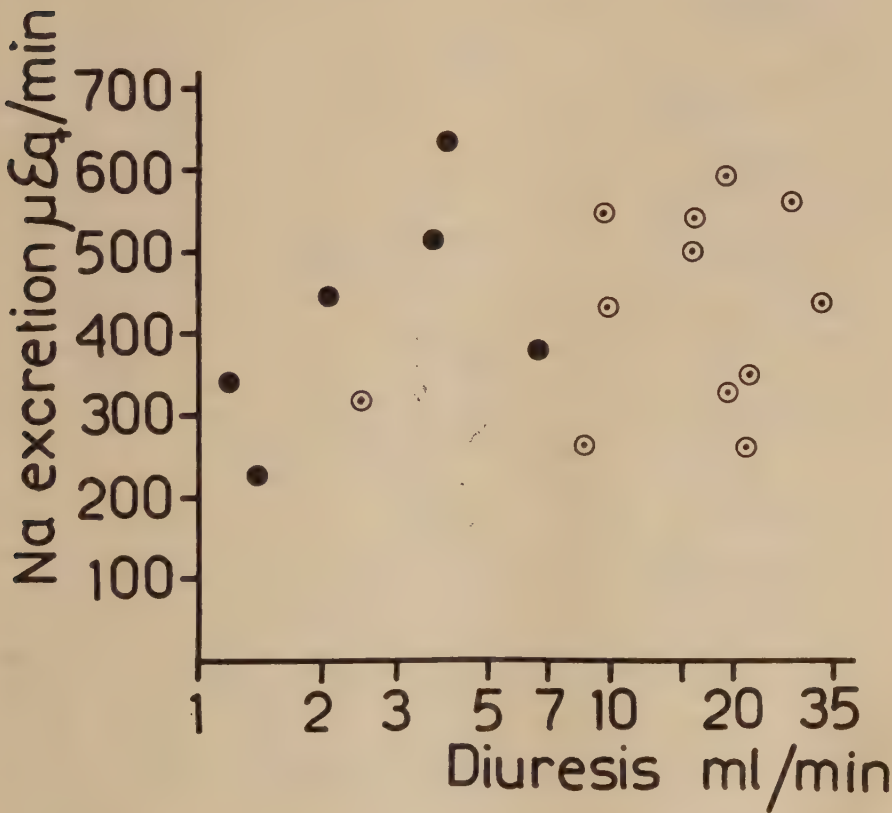


Fig. 5. Sodium excretion (linear) plotted against diuresis (logarithmic) from the values registered in table 10 (normal subjects). Black dots “basal” periods, the ring-dots values obtained during rapid infusion*.

* It has been tested whether the gradient of the regression line of sodium on log diuresis can differ from zero only due to sampling variation. That is the case.

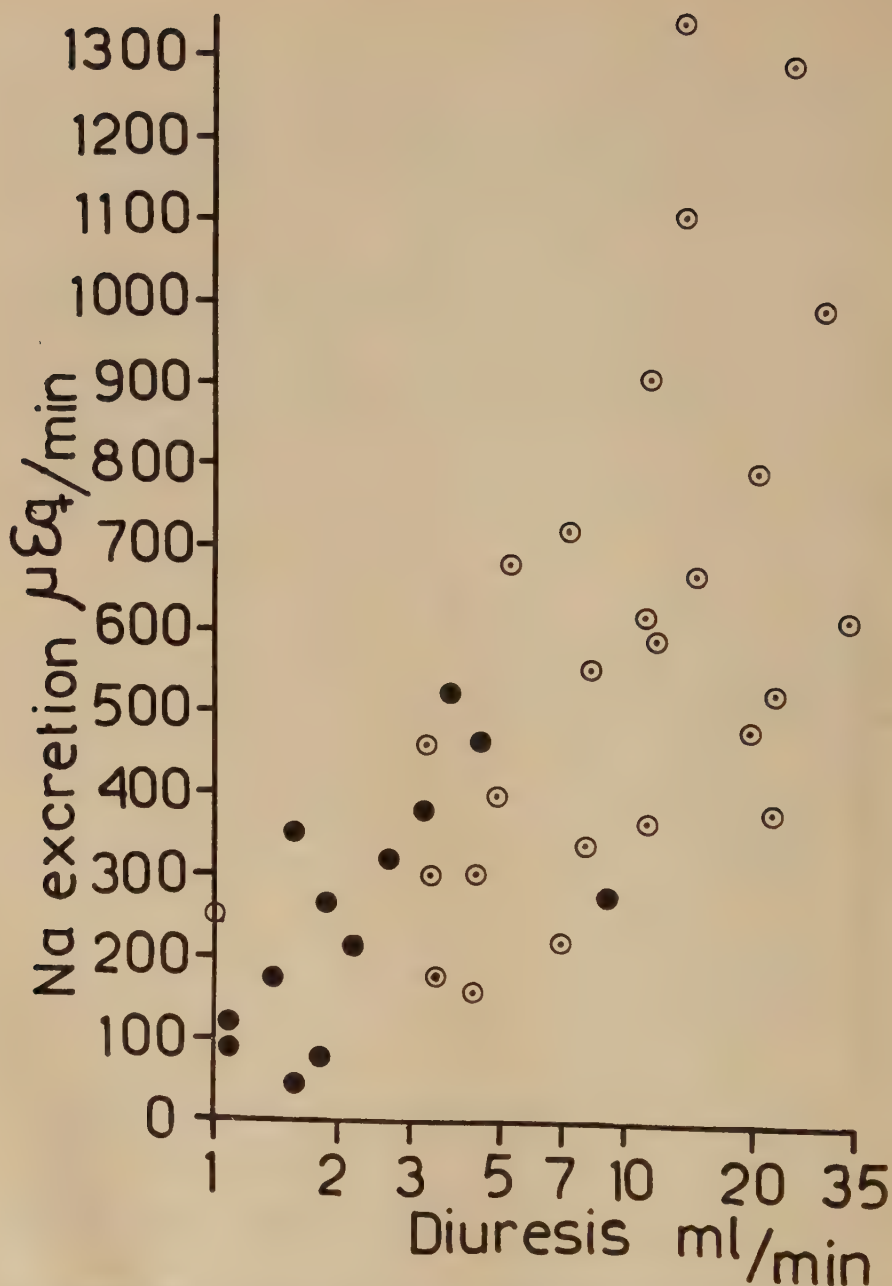


Fig. 6. Sodium excretion (linear) plotted against diuresis (logarithmic) from the values registered in table II a (patients with "essential" arterial hypertension). Legend as in fig. 5*.

* The formula of the regression line of sodium excretion (Na) on $\log_{10}$ diuresis ($\log D$) is: $\text{Na} = 95 + 498 \log D$. It has been tested whether the regression coefficient can differ from zero only due to sampling variation. This is highly improbable ($t = 5.59$; degrees of freedom = 37). Note that the "basal" values, though varying widely (through prehydration ?) nevertheless seem to lie on the same line as the other values.

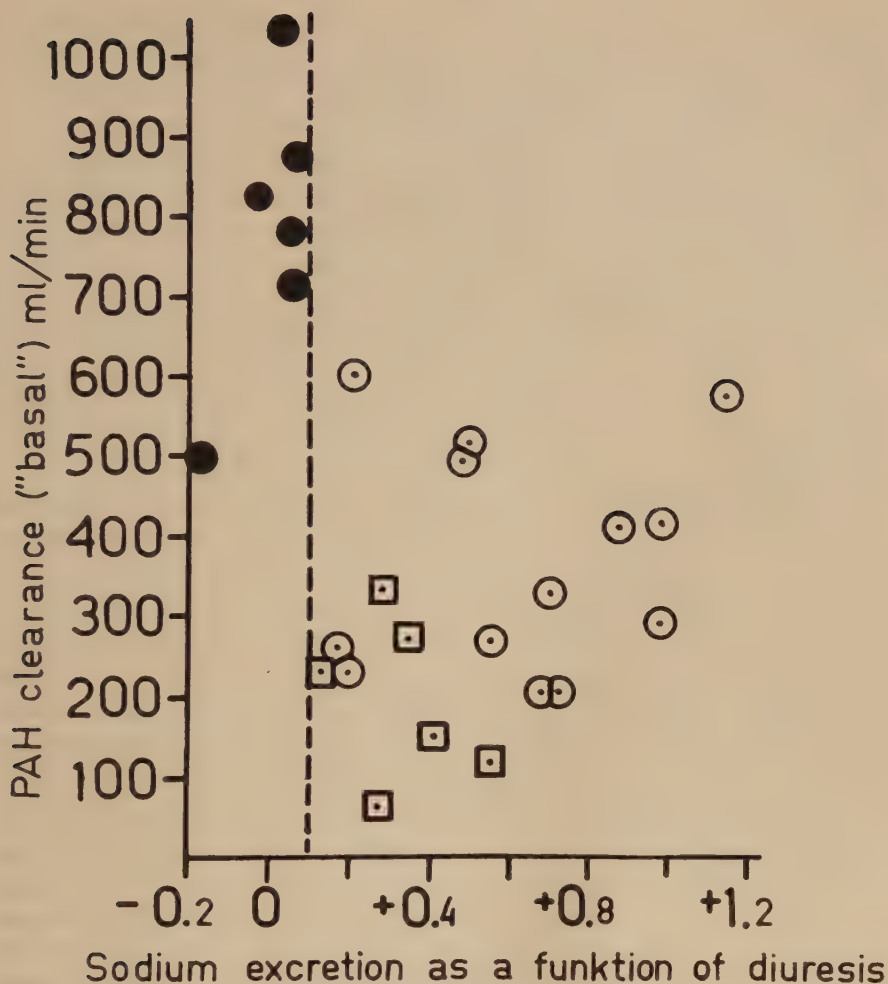


Fig. 7. The values of the "gradients", calculated as described in text, for sodium excretion as a function of the diuresis plotted against the "basal" PAH-clearance values. Black dots normal subjects, ring dots cases of "essential" arterial hypertension, squares cases of "non-essential" hypertension. The broken vertical line is drawn to point out the striking difference between the normals and the hypertensives*.

* It has been tested whether the group of gradients to the left of the broken line may be regarded as belonging to the same population as those to the right of the line. This is highly improbable. ($t = 4.19$; degrees of freedom: 22).

tive. The relative change in the sodium excretion¹ has been determined as a linear function of the relative change in the diuresis¹ (for the three periods accounted in tables 10—12). The gradient for the linear function of the indi-

¹ "Basal" value = 1.0.

vidual case has been taken as a measurement of the companionship between water and sodium in the urine. Fig. 7, where these gradients are represented, shows two things: that in the presented material patients with arterial hypertension have a consistently higher gradient than the normal subjects of experiment, and that among hypertensive patients there does *not* appear to be any correlation between the PAH clearance on the one side, and the companionship between sodium and water in the urine on the other. PAH clearance is chosen as a measure of the renal function as it is the first which appears to decrease during hypertension.

Although the present material is too small to permit the drawing of any definite conclusion, it may be tentatively assumed that cases of arterial hypertension develop in the course of their disease a *qualitative* change in their salt-water metabolism, seemingly independent of the severity of the hypertension.

The correlation between the diuresis and the sodium (or chloride) excretion in patients with hypertension has earlier been pointed out by Farnsworth and Baker (1943 a, 1943 b) Farnsworth (1946) and—in a small material—by Weston, Hellman, Escher, Edelman, Grossman, and Leiter (1950). Farnsworth (1946) reached the conclusion that the chloride excretion of patients with arterial hypertension is always greater than that of normals, if it is measured in proportion to the inulin clearance. This would entail that patients with hypertension, at least those with well-retained inulin clearance, would constantly be losing abnormally large quantities of chloride, and would be compelled to make up for this loss by a more than ordinary supply of sodium chloride in the diet. This seems improbable in particular for hospitalized patients. It is significant, however, that the smallest diureses with which Farnsworth worked, were seldom low diureses. If, for instance, in the present paper, the diuresis values in figs 6 and 5, which are less than 4 ml/min. were to be omitted, it would be easy to draw the erroneous conclusion that patients with hypertension had a higher sodium excretion than normal subjects of experiment. As, under normal conditions, hypertensive patients have by no means a higher diuresis than normals, Farnsworth's results do not support the assumption that these patients have a higher sodium excretion or sodium metabolism than normals.

From the data which are presented in this paper it seems as though a more comprehensive description should be as follows: patients with hypertension, not uncompensated, excrete during high diuresis more sodium than normal subjects, but during low diuresis their excretion of sodium is less than that of normals.¹ The data which are accounted for in tables 10, 11 a and 12 a

¹ Salt loading and a »salt free» diet can probably cause exceptions from this rule.

indicate that chloride excretion is, in all important respects, parallel with the sodium excretion.

As has been pointed out earlier, Brodsky and Graubarth (1953) have shown that patients with essential hypertension react with a larger excretion of salt than normals to analogous mannitol-loading (*i. e.* osmotic diuresis). In my experiments, however, sodium excretion increased as much in cases where no glucose was excreted during the experiment as it did in the cases where glucosuria occurred. The difference in reaction between normal subjects of experiment and patients with hypertension can obviously not be explained away as caused by a different "sensitivity" to osmotic diuresis.

Inulin clearance and sodium excretion

Another basis of explanation of the varying reactions in normals and in patients with arterial hypertension is that the latter, speaking relatively, increased their inulin clearance more than the former after the commencement of the rapid infusion.

If one compares "the average mean curves" for the inulin clearance of normals with those of their sodium excretion (fig. 2 resp. fig. 4) one is struck by how steady the sodium excretion remains despite the changes in the inulin clearance. During the period 0—50 the product inulin clearance times sodium concentration in plasma (= "sodium load") increased on an average of 3,760 $\mu\text{Eq}/\text{min}$, while the sodium excretion increased simultaneously by only 11 $\mu\text{Eq}/\text{min}$. This is very difficult to explain if one considers filtration as being the dominating determinant for sodium excretion. On the contrary, these facts emphasize the correctness of Ekehorn's (1938) general thesis that filtration and reabsorption normally change in a reciprocal manner—and that these changes are intimately related to one another.

Not even as regards the hypertensive patients does sodium excretion appear to be greatly dependant on the filtration rate. During the first 50-minute period of the rapid infusion the average "sodium load" was 29 per cent higher than basal. The sodium excretion increased simultaneously by 99 per cent. During the second 50-minute period, however, the "sodium load" was only 4 per cent higher than during the first (the change is *not* significant); the increase of sodium excretion between the said periods was none the less 104 per cent ($p < 1 : 200$). As is shown by fig. 2 and fig. 4 the discrepancy is even clearer if one reckons with shorter periods than 50 minutes.

The above discussion can be summarized as follows: under the given conditions of experiment no connection in time between the increase of inulin clearance (resp. sodium load) and sodium excretion can be observed in normals. On the contrary, the increase of "sodium load" appears to be followed by a

compensatory increase of sodium reabsorption. In hypertensives, after the commencement of the rapid infusion, there occurs initially a considerable compensatory increase of sodium reabsorption, but this capacity for regulation lessens successively during the hydration experiment.

4. *Peroral fluid loading (beer resp. water).*

In all but one experiment (Hyp. 41, water) every case showed a more or less marked increase of sodium excretion when the diuresis was increased by reason of the peroral fluid supply. It should be observed that this rise did not reach the same order of magnitude as during the rapid infusion. It should be further emphasized that the excretion of sodium during the course of the experiment was sometimes markedly irregular, with large jumps from period to period, jumps which cannot reasonably have been caused by incomplete emptying of the bladder. These differences between the results of peroral fluid loading and rapid infusion are probably due to the different experimental conditions during both types of experiment. During the peroral loading experiments with water and beer, the supply of water was 1 litre per hour—during the rapid infusion experiments approximately 1.5 litres. During the peroral fluid loadings the patients were, for the most part, in a sitting position, but when emptying the bladder they were obliged, of course, to stand up. During the rapid infusion, the patients were always recumbent. This difference in position may well have affected the results. Finally—and this is probably most important of all—the difference in the manner of supply is fundamental. The intravenous fluid supply, even at the quick rate of 25 ml/min. is not even perceptible to the subjects of experiment. Peroral fluid supply, on the other hand, is tolerated (at the rate used here) very differently by different subjects. Certain individuals can stand a supply of fluid at this and even much greater speed without any sensation of discomfort. Others are very considerably affected. Patients who showed obvious discomfort during the first fluid-loading experiment were rejected as subjects of experiment before determination of the electrolyte excretion values. The fact remains, however, that certain patients can experience a more or less diffuse feeling of discomfort (possibly related to “the dumping syndrome”) during peroral fluid loading, and that this in itself can affect both the diuresis and the electrolyte excretion values.

The reasons given above support the assumption that patients with hypertension react in principle similarly with regard to electrolyte excretion, whether they have been supplied with glucose-containing fluid intravenously, or with glucose-free fluid (water or beer) perorally. The glucose as such appears to have no significance, while it is the supply of fluid which is decisive.

The limited material and the observations made above regarding experimental conditions make it difficult to determine whether patients with hypertension—as in the case of normals—(Ek and Josephson 1953 a) react with greater diureses and sodium excretions to a certain quantity of beer than to a corresponding quantity of water. The registered results are, however, more in favour of such an assumption than against it.

5. General remarks on the "companionship"

The supply of fluid has in itself a number of effects which are certainly connected with each other, but are nevertheless not identical. The most striking among these effects is expansion of the extracellular fluid compartment, the dilution of the solutes in plasma, and the increase of the diuresis.

In the cases of arterial hypertension which had developed a considerable diuresis the volume expansion of the extracellular fluid compartment at the end of the experiment should have been negligible or non-existent. Sodium excretion continued, however, to increase. Although this does not argue conclusively against the increase of sodium excretion having been caused by expansion of the extracellular fluid compartment, it makes this alternative less probable.

That a dilution of the plasma solutes, including sodium, should be able to cause increased sodium excretion seems at a first glance to be absurd, but similar paradoxical reactions have nevertheless been established. Roemmelt, Sartorius and Pitts (1949) showed in adrenalectomized dogs that these, during high plasma concentration of sodium, reabsorbed more sodium than was normal in the tubuli, so that the sodium excretion was disproportionately low. If the plasma concentration was low, the sodium excretion became, on the other hand, abnormally high. Similar paradoxical reactions can also be found in patients with cardiac edemas (Weston, personal communication). Dilution of plasma cannot, therefore, *a priori* be excluded as a cause of the increase in sodium excretion which appears in patients with arterial hypertension during rapid infusion or peroral fluid loading.

The mechanism for the increased sodium excretion after rapid infusion resp. peroral fluid loading may well be deduced as follows: the sodium excretion in patients with hypertension is directly dependent on the diuresis, and the kidneys of these patients have a reduced ability to reabsorb *separately* sodium resp. salt; they have, in other words, an insufficient concentration and dilution capacity with regard to sodium (not identical with isosthenuria¹). In most of the reported experiments the correlation between the

¹ Thus, the specific gravity of the urine varied widely during the experiments. The concentration of urea was determined in a limited number of urine samples from hydration experiments. The ratio urea conc./creatinine conc. was found to be rather constant.

diuresis and the sodium excretion was good. It appears, therefore, as if the diuresis changes in themselves are the cause of the observed changes in sodium excretion in hypertensives. Against this, however, is the fact that Ek, Bucht and Werkö (1954) found that in individual cases the sodium excretion in hypertensives could continue to increase during the rapid infusion, even after the diuresis had stagnated or decreased (see Ek, *et. al.*, fig. 4—corresponding case hyp. 3, table II a in this paper).

No definite or basically sound explanation or hypothesis regarding the findings can be given at present. A few brief, unpretentious statements may, however, be made here.

a) The quick reaction with regard to electrolyte excretion on the rapid infusion makes it extremely improbable that the results depend upon a reaction in the adrenal cortex. Theoretically one might assume that the rapid infusion, through one of its direct effects, could alter the reaction of the kidney towards corticoids circulating in the blood—"a conditioning" according to Selye's terminology (1952).

In the experiments related here, a rapidly commencing fluid supply and a rapid reaction of the kidneys has been aimed at. The purpose of this has been, *inter alia*, to exclude as far as possible the influence of corticoids.

b) It is reasonable to assume that ADH (antidiuretic hormon) concentration in the blood decreases during the rapid infusion and that this decrease influences the size of the diuresis. On the other hand it is extremely improbable that a decrease in ADH concentration can have causal connection with the increased sodium excretion of the hypertensives (other than perhaps indirectly, in the degree in which diuresis and sodium excretion are connected). On the contrary, ADH is considered by many authors to have a chloruretic effect. A decrease of ADH concentration in the blood should, therefore, result at first hand in a decreased excretion of chloride (sodium). The assumption that ADH in physiological doses is chloruretic has certainly been criticized (Van Dyke 1950, Shannon 1950) but there is still less reason to believe that the contrary is the case. There is therefore no reason for supposing a reduction of the blood concentration of ADH to be the direct cause of the increased excretion of sodium in the hypertensives.

c) As is known, noradrenaline and adrenaline reduce the renal blood flow and the sodium excretion. Cannon, McIver, and Bliss (1924), Euler and Luft (1952) and Dunér (1953) have found an "antagonism" between the glucose content of the blood and the incretion of catechols from the adrenal glands. The question therefore arises as to whether the results reported here can be explained by a blockage or reduction of the noradrenaline-adrenaline production by the glucose-containing rapid infusion. For a study of this problem

the catechol content of the urine would have to be determined during very short (at most 20 minutes long) periods. A considerable excretion of noradrenaline-adrenaline would therefore be required. Such an excretion is not unusual in arterial hypertension. Euler, Hellner, and Burkhold (1954) have shown that 16.4 per cent of patients with arterial hypertension have increased excretion of noradrenaline. In a number of my cases the noradrenaline/adrenaline excretion has been determined at the Department of Physiology, Karolinska Institutet. As is shown by table 6 a, all the cases of arterial hypertension hitherto examined have happened to belong to a group which had normal excretion. The examination of a case of hypertension with high excretion of noradrenaline/adrenaline would be of the greatest interest.

d) Finally it should be pointed out that both salt and water excretion can be affected via the renal nerves, apparently quite independently of hormonal changes. Balakschina (1936) has shown that in a hypophysectomized dog with one kidney denervated, the urine volume produced by the intact kidney can both increase and decrease due to conditioned reflexes, while the excretion from the denervated kidney remains steady. Kaplan, Fomon and Rapoport (1951) studied mannitol-loading in dogs whose greater splanchnic nerve was divided on one side. The sodium and chloride concentrations (in common with the total excretion of these ions) were larger in the urine from the denervated side.

As mentioned earlier some of the patients in the present material had been sympathectomized according to Smithwick or Peet. These patients reacted in the same way as those not operated.

Irrespective of the reason why cases with arterial hypertension react to rapid infusion in a manner different to normals, the significance of this reaction in hypertensives should be discussed.

As the "companionship" was found in patients with "essential" hypertension, as well as in "non-essential" and in cases of mitral stenosis (Werkö, Ek, Bucht, Varnauskas 1954) it seems to be a result of the disease itself and not an etiologic factor. This is further supported by the fact that there does not seem to be any correlation between the degree of "companionship" and the degree of disease. (Fig. 7.)

Judging from the present material it would seem as though patients with arterial hypertension

- a) had markedly low sodium excretion during low diuresis
- b) reacted, in some cases, during fluid loading with markedly low diuresis.

Should these two characteristics become further pronounced the result would be a marked inability to excrete sodium and water. This would

mean that patients with arterial hypertension carry a seed of edema and incompensation within them even during the earliest stages of the disease.

If, on the other hand, tendencies to a low diuresis response to water loading were allayed, the companionship between sodium and water in the urine could be put to advantage. Patients with arterial hypertension could then be depleted of salt by a plentiful supply of fluid.

6. *Potassium metabolism*

a) *Potassium concentration* in plasma fell, during the rapid infusion, both in normals and in patients with arterial hypertension (tables 10—14). The decrease was so similar, that the material in tables 10, 11 and 12 can be combined in one group. If the concentration during the basal periods is taken as a starting point, the potassium concentration in plasma sank during the first 50-minute period on an average of 12 per cent in all 25 experiments (normals and hypertensives). During the second 50-minute period it sank by 18 per cent. Corresponding reductions in the sodium concentration were 5, resp. 6.5 per cent. This striking difference between the decrease in potassium and sodium concentration cannot be explained by the fact that the potassium excretion in the urine was relatively larger than the sodium excretion compared with the plasma concentrations. It depends with all probability on the supply of glucose which, according to a number of authors, specifically reduces the potassium concentration in plasma (Flock, Bollman, Mann, and Kendall, 1938, and Forber, Pellegrino, Conan and Earle, 1951).

b) *The urine excretion of potassium in normals* sank during the rapid infusion in a characteristic manner. While remaining practically unchanged during the first 50-minute period, it fell during the second 50-minute period on an average of 41 per cent. $\frac{U}{P}$ ratio for potassium sank then often below 1.0.

The smallest registered $\frac{U}{P}$ ratio was, for the 6 normal cases in table 10, and (before the Oxyphyllin injection) for the 3 normal subjects who were only used for the Oxyphyllin experiments: A₁: 0.51, A₂: 0.55, A₃: 0.61, B₁: 0.93, B₂: 0.27, B₃: 0.59, B₄: 1.20, B₅: 0.50 and B₆: 0.46. Homer Smith (1951) declared that $\frac{U}{P}$ ratio lower than 1.0 never has been registered.¹

Under the experimental conditions in my experiments, the $\frac{U}{P}$ ratio for potassium appears in general to fall considerably below 1.0. This should mean that potassium can *either* be *actively* reabsorbed in the tubuli *or* that water

¹ That was debatable even then.

is secreted by the distal tubuli. An active reabsorption of potassium is presupposed by several authors (Berliner 1951) and the possibility of a distal tubular water secretion has also been discussed (West, Kaplan, Fomon and Rapoport 1952).

c) *Potassium excretion in cases of arterial hypertension* followed (far more than in normals) a varying pattern during the rapid infusion. A number of cases followed, in the main, normal subjects in this respect. In 7 experiments of $19 \frac{U}{P}$ ratio for potassium sank noticeably below 1.0. In many experiments (see tables 11a and 12a) the potassium excretion per minute sank during the second 50-minute period. In some of the cases, however, the excretion values for potassium *rose* during the second 50-minute period of the rapid infusion. Neither a specially high diuresis nor a specially high increase of inulin clearance was characteristic for these cases. However, in all the five cases (tables 11a and 12a) who showed a sodium excretion exceeding $1,000 \mu \text{Eq/min.}$ during the second 50-minute period, the potassium excretion rose simultaneously.

It has long been known that an increased supply of salt under a number of different experimental conditions increases the potassium excretion. Kruhøffer (1950) has shown that this increase can occur despite a steady inulin clearance and a decreasing plasma concentration of potassium. He connects this with the increasing diuresis (or rather the "decrease of the calculated proximal reabsorption percentage of water").

From my findings it appears as though high sodium excretion as such tends to increase potassium excretion (by means of a distal ion exchange mechanism?) Kruhøffer's findings might therefore, as I understand them, equally be interpreted as the result of an increased sodium excretion. It is conceded, however, that my material is too small for strict mathematical treatment, and that the results are obtained from a pathological material.

II. Experiments with supply of a diuretically active purine derivative during the course of strong hydration

A. Results in normals

It has long been known that a large number of purine derivatives have a diuretic and natriuretic effect. (For a survey of literature see Smith 1951.) In this laboratory we have earlier studied the effect of a diuretically effective theophylline derivative, theophyllin-1-aminopropanol-(2), on the clearance values in a normal material (Ek and Josephson 1953 b). The results can be summarized as follows: Oxyphyllin gave a marked increase of inulin clearance, at least immediately after the (Oxyphyllin) injection. On the other hand, the

increase of PAH clearance and endogenous creatinine clearance was questionable, or relatively small. The experiments presented in table 16 confirm this results in all essentials. In our previous experiments attention was drawn to the observation, that the ratio inulin clearance/creatinine excretion increased during the supply of Oxyphyllin.

Several alternative explanations of this observation were discussed in the above-mentioned paper. The following explanation, however, was not put forward: the large inulin molecules pass the glomerular membrane more slowly than water, *i. e.* inulin clearance gives a measurement of ultrafiltration which is too low. If the supply of Oxyphyllin increases the permeability of the glomerular membranes, inulin clearance would approach or become identical with glomerular filtration rate. It ought to be possible to test, for instance according to Wallenius (1954), whether this hypothesis is true or not. His method implies a measurement of the influence of the molecular size, on the clearances of dextrans.

The main reason for the undertaking of the Oxyphyllin experiments is illustrated by the following preliminary experiment. A normal man was given $\frac{1}{2}$ a litre of water to drink every fifteenth minute (corresponding to 33 ml/min.) during several hours. The diuresis rose successively until after a bout 1 hour it had become approximately 18 ml/min. Although it was anticipated that the subject during the course of the experiment retained water, and although the concentration of hemoglobin in the blood fell, the diuresis did not rise further. When, however, 10 ml of Oxyphyllin was given intravenously the diuresis leapt up from approximately 18 to approximately 30 ml/min. The experimental conditions of this test were unsuitable from several points of view. The experiment gave rise, however, to a number of questions:

a) Can purine derivatives increase the diuresis still further when by means of a considerable fluid supply the latter has risen to an apparently maximum level?

b) Assuming that an almost instantaneous, large increase of this kind in the diuresis can be obtained—how then has this “extra volume” been treated during the passage through the tubuli? Do the changes of the urine volume passing the tubuli cause a change of the reabsorption (or secretion) of solutes in the tubuli? Or does the chemical composition of the “extra volume” resemble the glomerular filtrate in important respects?

Ad a) It is obvious from table 16 that the diuresis increases almost instantaneously after the Oxyphyllin injection—even when the diuresis is a “maximum” water diuresis. During the experiment one can even see how the drop frequency from the bladder catheter rises during the actual injection.

Ad b) The urine which is emptied from the bladder must, at least during the first "Oxyphyllin period", be a mixture of two chemically dissimilar kinds of urine (the "washing-out" effect mentioned above). The period immediately preceding the Oxyphyllin supply must therefore be compared with the *second* Oxyphyllin period. When this period begins one can presume that nearly all the urine formed before the Oxyphyllin supply had been rinsed away from the urinary tracts (observe the extremely high diuresis values).

Table 24. The observed increase in ml/min. of the diuresis after injection of a theophylline derivative given during "maximal" diuresis due to a rapid infusion. The observed increase is compared with that calculated as described in text from the sodium, potassium and chloride concentrations in urine and plasma.

Exp. No.	Increase of diuresis	«Sodium volumes»	«Potassium volumes»	«Chloride volumes»
A 1.....	14.0	17.0	20.0	15.2
A 4.....	13.7	7.4	28.6	6.7
A 5.....	13.0	9.7	13.4	8.6
A 6 = B 3.....	3.0	5.8	6.0	5.8
A 7 = B 4.....	10.1	3.8	9.0	3.7
Mean.....	10.8	8.7	15.6	8.0

As an attempt to study how the "extra volume" of urine was treated by the tubuli the following calculations were made. Subtract the diuresis from the last period before the Oxyphyllin supply from the diuresis during the second Oxyphyllin period. Divide the difference in sodium excretion between the same two periods with the sodium content in plasma, and repeat this operation with regard to potassium and chloride. There will then be (see table 24) four different "volumes" to compare. If the "extra volume" really had been an ultrafiltrate, the three "electrolyte volumes" would obviously be practically identical with the diuresis increase. Both the first and second "Oxyphyllin" periods were of different length from experiment to experiment. The values in table 24 are thus not altogether comparable. Further: the different "electrolyte volumes" are calculated from the *difference* between two excretion values. Thus the sources of error are great. Finally: it is seen from table 16 that in all the experiments except A₇ (B₄) the diuresis during the first "Oxyphyllin period" was higher than during the second.

This, in common with the rapidly changing urine pH values, indicates that the normal kidney quickly organizes a number of adaptive mechanisms after the "surprise" caused by the instantaneously increasing flow through the

tubuli. These "adaptive mechanisms" may be different for different substances in the urine. Further, their onset may be different, too.

Despite all these complicated circumstances table 24 appears to show that the diuresis which is caused by the supply of Oxyphyllin initially resembles, in important respects, a glomerular ultra filtrate.¹ However, the table may also be in accordance with the above-mentioned hypothesis of "adaptive" processes quickly coming into effect. These "adaptive" processes are in time and/or order of magnitude: reabsorption of chloride, of sodium, of water and finally of potassium. This, as has been indicated several times above, is a purely hypothetical argumentation.

In certain respects the effect of Oxyphyllin resembles that of a carbonic anhydrase inhibitor.

B. Results in patients with hypertension

The supply of Oxyphyllin to patients with arterial hypertension (see table 17) during the course of strong, intravenous fluid loading gave in 3 cases out of 5 results which were analogous for the most part with those obtained in normal subjects: the "diuresis roof" *i.e.* the diuresis which seems to be maximum during strong fluid loading was broken through almost instantaneously by the Oxyphyllin injection, and in relation to this the electrolyte excretion showed a strong increase. If the diuresis increase and the virtual electrolyte volumes are calculated according to the same rules as in table 24, the following results will be obtained. Case "Hyp. 6": diuresis increase 5.2, "sodium volume" 6.1, "potassium volume" 8.3 Case "Hyp. 32" diuresis increase 8.3, "sodium volume" 5.7. Case "Hyp. 14" diuresis increase 11.3, "sodium volume" 6.2. All volumes (including diuresis increase) are expressed in ml/min. Similar volumes cannot be worked-out for cases "Hyp. 10" and "Hyp. 17"; the diuresis here during the second Oxyphyllin period was namely lower than during the last period before the Oxyphyllin injection.

Case "Hyp. 10" did not seem to react at all to Oxyphyllin as regards the renal function. If anything, the Oxyphyllin seems to have had an antidiuretic effect after several minutes. It has long been known that the natriuretic effect of purine derivatives lasts longer than the diuretic. Case "Hyp. 10" is the only case in table 17 which did not appear to react initially to Oxyphyllin. The same phenomenon has, however, been observed in patients with compensated mitral stenosis (unpublished observations). Davis and Shock (1949) found also that theophyllin ethylene diamine had an extremely

¹ Here, as in the previous calculations, no consideration has been given to the Donnan effect and to the protein volume in plasma.

variable effect on the clearance values, sodium excretion and diuresis of patients in congestive failure. Sometimes there was no effect at all.

Case "Hyp 17" did not despite 88 minutes of the rapid infusion reach a higher diuresis than 3.0—3.7 ml/min. The slight temporary increase in the diuresis which followed on the Oxyphyllin injection soon changed to a marked decrease. This was probably connected with the fact that during the second Oxyphyllin period the patient had a short "black out", accompanied by convulsions (the result of a summation of water intoxication and the strong centrally stimulating effect of the Oxyphyllin?).

With regard to clearance values after the administration of Oxyphyllin to patients with arterial hypertension, the inulin clearance increased in every case, usually—as in normals—more than the creatinine excretion (see particularly case "Hyp. 14", table 17).

PAH clearance also increased on the administration of Oxyphyllin to these patients. This cannot, however, be definitely ascertained, on account of the results of the washing-out phenomenon. Further, it should be pointed out that the material is very small—chiefly because the complications described above in case "Hyp. 17" necessitated extreme caution.

GENERAL CONCLUSIONS

The above argumentation and the observations related have given rise to varying opinions and conclusions which are briefly summarized below. It must, however, be emphasized that these are, to a large extent, of a purely hypothetical nature.

In both normals and in patients with hypertension the inulin and PAH clearance increase quickly when the patients receive a rapid intravenous fluid supply (approximately 25 ml/min.). This is probably due to a rapid expansion of the extracellular fluid compartment.

Under these experimental conditions both the relative and the absolute clearance values of patients with hypertension seem to increase more than do those of normal subjects. It is probable that in most cases the extracellular volume in hypertensives increases more than in normals. This presumed difference may contribute to the fact that the clearance increase is greater in hypertensives. A more important cause of this difference, however, is probably the fact that the kidney vessels in patients with hypertension have a pathologically high and—at least in the early stages of the disease—reversible tonus. This is dissipated by the infusion.

Both the sodium and the chloride excretion in patients with arterial hypertension seem to follow a fundamentally different pattern than in normal subjects. In the former group, the sodium excretion per minute is more or less directly dependent on the diuresis—in the latter group the sodium excretion is, in all essentials, independent of the diuresis.

Patients with arterial hypertension react in a typical manner, irrespective of the degree of severity of the disease and irrespective of whether the hypertension should be called “essential” or “nephrogenic”. (Patients with mitral stenosis react in a similar way.)

This makes it probable that the established “companionship” between

water and sodium is not a cause of the arterial hypertension, but a result of the latter. It can, however, be of significance for the continued course of the disease, particularly incompensation.

Some patients with arterial hypertension, though not all, react with a relatively low diuresis increase to fluid loading (intravenous or peroral). Should this tendency and the above-named "companionship" become more pronounced, a patient with arterial hypertension would in all probability become edematous. To explain the "companionship" between sodium and water in the urine by a general kidney damage is not elucidating. It would seem more exact to describe it as a presumably functional incapacity to concentrate resp. dilute electrolytes in proportion to water in the tubuli. This incapacity is not synonymous with isosthenuria.

It is extremely difficult to explain the pattern of sodium excretion in both normals and patients with arterial hypertension if one assumes that filtration or, more correctly, inulin clearance is the dominating determinant. On the contrary, both the registered results as well as earlier investigations—even if interpreted otherwise by the authors (White, 1950, Blake, Wegria, Ward, and Frank, 1950, Selkurt 1951, Tompson and Pitts 1952)—support the theory that should any process at all be called a dominating determinant, this should be the tubular reabsorption rather than the glomerular filtration. In all probability it is fundamentally wrong to define any one of the various processes in the kidney as "the most important" for sodium excretion. It is, instead, most likely that filtration and reabsorption are intimately related to and dependent on one another.

In accordance with this it is very questionable to assume, that any part of the tubuli has any fixed—whether absolute or relative—capacity to reabsorb water or electrolytes. It cannot even be considered as proved that *any* individual electrolyte always stays at the same concentration as in the blood plasma in all parts of the proximal tubuli.

In both normals and patients with arterial hypertension the potassium concentration in plasma falls much more than does the sodium concentration during rapid infusion of glucose-containing fluid. The greater fall in the potassium concentration probably depends on the specific effects of the administered glucose. The urinary excretion of potassium sinks consistently in normals during the latter part of the rapid infusion. As a rule $\frac{U}{P}$ ratio for potassium then sinks below 1.0. A number of patients with arterial hypertension follow in all essentials the same pattern as the normals. In some patients, however, the potassium excretion increases during the corresponding

period. It appears as though this increase were caused by particularly high sodium excretion in the urine.

Oxyphyllin (purine derivative) seems to cause a large amount of urine—resembling ultra filtrate—to reach the urinary tract. The tubuli appear to adjust themselves quickly to the new burden. The kidneys of patients with arterial hypertension seem to react, although not always, in the same way as those of normals to Oxyphyllin.

Peroral fluid supply seems in principle to result in an increase of the sodium excretion similar to that achieved by rapid intravenous infusion. It has not been possible to register any established difference between the supply of beer and that of water in the present, limited material. Irrespective of this it would be of value to investigate whether ample peroral fluid supply is of advantage in the treatment of early, still compensated cases of hypertension. In this connection one should not be guided by the results of “acute” experiments alone. Here, long-time experiments are more important. Consideration should also be given to the patient’s subjective appreciation of the extra fluid supply, and the degree in which this appreciation influences the results and the possibilities for the practical carrying-out of such a supply.

Similarly, it would be of considerable interest to investigate whether hydration by ample fluid supply (see foot note page 51) (via sodium depletion?) really has a reducing effect on the blood pressure.

SUMMARY

The purpose of the investigation was to study the effect of strong hydration resp. diuresis increase on the kidney function and on the excretion of strong electrolytes, both in normals and in a material of patients with compensated hypertensive cardiovascular disease.

The following experiments were accordingly carried out:

a) After the inulin and PAH clearances and the excretion of sodium, potassium, chloride and creatinine had been determined during 2—3 “basal” periods, the subject of experiment received a rapid intravenous infusion (ca. 25 ml/min.) containing 3—5.5 percent glucose, with or without the addition of insulin.

The above-named clearances and excretion values were followed during the process of infusion for at least 100 minutes.

These experiments were carried out on six normal subjects of experiment and in eighteen cases (nineteen experiments) of arterial hypertension.

b) When the diuresis—after rapid infusion, as in a)—had stabilized itself at a high level, 0.35 g theophyllin-1-aminopropanol (2) was given. The clearances and excretion values were thereafter followed (still during the course of rapid infusion) for 2—3 periods.

These experiments were carried out on five normals and five cases of arterial hypertension.

c) Six patients with arterial hypertension were given 2 litres of water to drink during a period of two hours, and were asked to void their bladders spontaneously as often as possible. Exactly the same procedure was repeated with the same patients, although with one difference; the two litres of water were replaced by 2 litres of Swedish Pilsner beer (2.8 per cent alcohol).

During these experiments only the urine volume and the electrolyte excretion were followed.

Certain analytical problems which may be of interest in this connection were investigated and discussed.

The results of the experiments outlined in a), b) and c) are, briefly, as follows:

1) Both in normals and in patients with hypertension the values for the inulin and PAH clearances rise shortly after the commencement of the rapid infusion—in hypertensives the increase is relatively higher.

2) In normals the sodium excretion is *not* affected by the infusion. The patients with arterial hypertension react in a different way. Here a successive and powerful increase of the sodium excretion is registered, an increase which appears to run parallel with the diuresis ("companionship between sodium and water in the urine") although *not* with the inulin clearance. The chloride excretion appears to follow the excretion of sodium.

3) Hypertensive patients who receive peroral fluid loading (beer or water) seem to react with an increased sodium and chloride excretion. This reaction is analogous to that caused by a rapid intravenous infusion.

4) Normals who have received a rapid infusion show (towards the end of the infusion) a decreased potassium excretion. The $\frac{U}{P}$ — ratio for potassium is thus for the most part less than 1.0.

A number of hypertensives react in this respect analogously to normals. Others, on the other hand, show an increase of the potassium excretion during the infusion.

5) On the administration of theophyllin 1-aminopropanol-(2) during the process of a rapid infusion, there is a further abrupt increase of the diuresis, even though the latter seems to have already stabilized itself at a high level. In this way diuresis values of up to 50 ml/min are obtained. The increase of the clearances of sodium, potassium and chloride are of the same order of magnitude as the diuresis increase.

It appears that under analogous experimental conditions most patients with hypertension react in the same way as normals to the administration of theophyllin-1-aminopropanol-(2).

A discussion of the findings resultant on the experiments is summarized in "General Conclusions" (page 68).

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